Chapter 3 --Basic Neurobiological and Preclinical Research

Over the past decade, basic neurobiological research has enhanced our understanding of the biological and genetic causes of addiction. These discoveries have helped establish addiction as a biological brain disease that is chronic and relapsing in nature (Leshner, 1997). By mapping the neural pathways of pleasure and pain through the human central nervous system (which includes the spinal cord and brain), investigators are beginning to learn how abused psychoactive drugs, including alcohol, interact with various cells and chemicals in the brain. As scientists increase their knowledge, medications are being designed to reverse, control, or minimize the negative effects of substance abuse (Charness, 1990; Kuhar, 1991; National Institute on Alcohol Abuse and Alcoholism [NIAAA], 1994).

Fundamentals of the Nervous System

The human nervous system is an elaborately wired communication system that networks the entire body, and the brain is the central communications center of this system. The brain processes sensory information from throughout the body, guides muscle movement and locomotion, regulates a multitude of bodily functions, forms thoughts and feelings, and controls all behaviors. The fundamental functional unit of the nervous system is a specialized cell called a neuron, which conveys information both electrically and chemically. The function of the neuron is to transmit information: It receives signals from other neurons, integrates and interprets these signals and, in turn, transmits signals to other, adjacent neurons (Charness, 1990).

A typical neuron (see Figure 3-1) consists of a main cell body (which contains the nucleus and all of the cell’s genetic information), a large number of short-branched filaments called dendrites, and one long fiber known as the axon. At the end of the axon are additional filaments that form the connections with the dendrites of other neurons. Within neurons, the signals are carried in the form of electrical impulses. But when signals are sent from one neuron to another, they must cross a gap from one cell membrane to another. The gap at the point of connection between the neurons is called a synapse. At the synapse, the electrical signal within the neuron is converted to a chemical signal. The chemical messengers that transmit the signal are called neurotransmitters.

Neurons communicate with other neurons by releasing neurotransmitters, which travel across the synapse and bind or adhere to specially formed receptors that are lodged on the outer surface of the target neuron (Charness, 1990). Approximately 50 to 100 different endogenous neurotransmitters, with one or many binding sites or receptors, have been identified in the human body. Figure 3-2 illustrates a typical synaptic connection and depicts the chemical communication mechanism. Neurotransmitters may have different effects depending on the subtype of receptor activated. Some increase a receiving neuron’s responsiveness to an incoming signal—an excitatory effect—whereas others may diminish the responsiveness—an inhibitory effect. The responsiveness of individual neurons within the brain affects how the brain functions as a whole (how it integrates, interprets, and responds to information), which in turn affects the function of the body and the behavior of the individual. The accurate functioning of all neurotransmitter systems is essential to ensure normal brain activities (NIAAA, 1994; Hiller-Sturmhöfel, 1995).

Neurological Reinforcement Systems And Drug Dependence

Psychologists have long recognized the importance of positive and negative reinforcement for learning and sustaining particular behaviors (Koob and LeMoal, 1997). Beginning in the late 1950s, scientists observed in animals that electrically stimulating certain areas of the brain led to changes in mental alertness and behavior. Rats and other laboratory animals could be taught to self-stimulate pleasure circuits in the brain until exhaustion. If cocaine, heroin, amphetamines, or nicotine were administered, for example, sensitivity to pleasurable responses was so enhanced that the animals would choose electrical stimulation of the pleasure centers in their brains over eating or other normally rewarding activities. The above process in which a pleasure-inducing action becomes repetitive is called positive reinforcement. Conversely, abrupt discontinuation of alcohol, opiates, and other psychoactive drugs following chronic use was found to result in discomfort and craving. The motivation to use a substance in order to avoid discomfort is called negative reinforcement. Positive reinforcement is believed to be controlled by various neurotransmitter systems, whereas negative reinforcement is believed to be the result of adaptations produced by chronic use within the same neurotransmitter systems.
Experimental evidence from both animal and human studies supports the theory that alcohol and other commonly abused drugs imitate, facilitate, or block the neurotransmitters involved in brain reinforcement systems (NIAAA, 1994). In fact, researchers have posited a common neural basis for the powerful rewarding effects of abused substances (for a review, see Restak, 1988). Natural reinforcers such as food, drink, and sex also activate reinforcement pathways in the brain, and it has been suggested that alcohol and other drugs act as chemical surrogates of the natural reinforcers. A key danger in this relationship, however, is that the pleasure produced by drugs of abuse can be more powerfully rewarding than that produced by natural reinforcers (NIAAA, 1996).

Unlike many other drugs of abuse (e.g., opiates, phencyclidine), alcohol does not interact with a specific receptor in the brain but appears to stimulate the release of many neurotransmitters (Koob et al., 1994). The development and persistence of alcohol dependence is a complicated process that is not yet completely understood. A number of lines of research are currently proceeding simultaneously to better understand the interaction between neurotransmitters and their receptors in encouraging drinking and the development of alcohol dependence (Froehlich, 1995). Investigations have recently confirmed that the key neurotransmitter systems that apparently interact with each other to mediate the reinforcing effects of alcohol include endogenous opioids, dopamine, serotonin, gamma-aminobutyric acid (also known as GABA), and the excitatory amino acid glutamate.

Alcohol and Neurotransmitters

Endogenous opioids, a class of neuropeptides that includes endorphins and enkephalins, produce euphoric, pleasurable effects such as "runner's high"; these neuropeptides also reduce sensitivity to pain. Heroin and morphine (which are called opiates; see Figure 3-3 for a comparison of opiates versus opioids) mimic the effects of endogenous opioids by stimulating opioid receptors. Alcohol also stimulates the release of endogenous opioids, which in turn activate the central dopamine reward system (Koob et al., 1994; Froehlich, 1996, 1997).

Dopamine produces immediate feelings of pleasure and elation that reinforce such natural activities as sex and eating in both humans and animals and motivates the repetition of these activities. Dopamine is believed to play an important role in reinforcement and motivation for repetitive actions (Di Chiara, 1997; Wise, 1982). Alcohol appears to increase dopamine release in a dose-dependent manner; that is, more dopamine is released when higher doses of alcohol are given (Nash, 1997; Ulm et al., 1995). It is believed that alcohol stimulates dopamine release via both indirect mechanisms (gustatory stimuli) and direct actions on the brain and that alcohol-induced stimulation of dopaminergic pathways in the brain may be at least partially controlled by the endogenous opioid system (Di Chiara, 1997; Froehlich and Wand, 1996).

Serotonin is associated with the reinforcing effects of many abused drugs through its mood-regulating and anxiety-reducing effects. Low levels of serotonin are associated with depression and anxiety.

Both animal and human studies have shown that alcohol administration increases levels of serotonin (LeMarquand et al., 1994; McBride et al., 1993). Selective serotonin reuptake inhibitors (SSRIs), a class of medications that includes fluoxetine (Prozac), increase serotonin concentrations in the brain. SSRIs have shown some efficacy in decreasing alcohol intake in both animals and humans (Ulm et al., 1995) and have shown some promise in treating alcohol-dependent adults (Naranjo et al., 1984, 1987, 1989, 1990). However, several small clinical trials have shown only modest effect of serotonergic agents in reducing alcohol consumption (Anton, 1995).

GABA is the primary inhibitory neurotransmitter in the central nervous system. Because alcohol intoxication is accompanied by the impaired coordination and sedation indicative of neuronal inhibition, researchers have investigated alcohol's effects on GABA and its receptors. The results of this research have shown that alcohol significantly alters GABA-mediated neurotransmission (for a review, see Mihic and Harris, 1997). GABA_A receptor antagonists block the ability of alcohol to cause ataxia (inability to coordinate muscle activity during voluntary movement) and anesthesia (Frye and Breese, 1982; Liljequest and Engel, 1982). Alcohol also potentiates the effects of GABA in the cerebral cortex and cerebellum (Suzdak et al., 1986; Allan and Harris, 1987).

Glutamate, an excitatory neurotransmitter, is associated with many learning, memory, and developmental processes. Alcohol normally inhibits the effects of glutamate. However, during abstinence following chronic alcohol use, excitation of the glutamatergic system is believed to have a role in alcohol withdrawal-induced seizures (Gonzales and Jaworski, 1997).
In addition to affecting neurotransmitters, it appears that chronic use of alcohol may alter the structure and functioning of neurotransmitter receptors that have roles in intoxication, reinforcement, and dependence. Alcohol also may alter signal transduction, which is the process of converting messages from the signaling neuron into changes in the target neuron. Alcohol dependence is also known to have a genetic component involved in vulnerability to drug abuse and dependence. Studies have found that identical twins, who share a common genetic heritage, are more likely to share addictions than fraternal twins, who share only half their genes (Pickens et al., 1991). Similarly, men with alcoholic fathers are three to five times more likely than men without any familial history of alcoholism to experience early onset of alcoholism or other drug dependence (Goodwin et al., 1973; Cloninger, 1987, 1988). Laboratory animals can be bred to show a greater preference for alcohol, compared with other strains of the same species (Froehlich, 1995; NIAAA, 1994, 1996). A number of recent lines of research have been focused on examining differences in the genes, as well as endogenous levels of various neurotransmitters, in rodents and humans differing in genetic predisposition toward alcohol dependence.

**Preclinical Research Linking Alcohol and Opioids**

For more than 100 years, careful observers have noted that alcohol and opiates produce similar pharmacological effects of euphoria and sedation, even though these drugs have very different chemical structures. A certain degree of cross-tolerance between these drugs has been demonstrated in animals: Morphine will relieve alcohol-withdrawal symptoms in mice, whereas alcohol suppresses withdrawal symptoms in morphine-addicted rats (Volpicelli et al., 1991). A Sears catalog from the early 1900s reflects the same phenomenon in humans by advertising an opium-based treatment for alcoholism and a tincture of alcohol for relieving the opiate (laudanum) addiction that was common among women of that era. In the 1970s, addiction specialists noted that opiate addicts would substitute alcohol for heroin when the latter was unavailable. In fact, opiates have often been described as a substitute drug for alcohol, and an increase in opiate availability has been reported to be accompanied by a decrease in alcohol drinking (for a review, see Siegel, 1986). Opiate addicts are known to increase alcohol consumption during withdrawal and decrease alcohol consumption during methadone treatment or when heroin or morphine is readily available and consistently used (Ulm et al., 1995; Volpicelli et al., 1991).

These observations and other research findings set the stage for more intensive preclinical investigations over the past 15 years into the links between alcohol consumption and both endogenous opioids and exogenous opiates. These studies found that

- Alcohol administration releases endogenous opioid peptides
- Important genetic differences exist in opioid response to alcohol consumption
- Opiate administration alters alcohol consumption
- Opioid receptor antagonists change alcohol consumption patterns

**Alcohol's Effects on Release of Endogenous Opioids and Opioid Receptor Activity**

For some time, scientists have suspected that alcohol stimulates release of endogenous opioids and affects opioid receptor activity. Alcohol consumption has been shown to stimulate the release of endorphins in both rodents and humans (Gianoulakis and Barcombe, 1987; Gianoulakis and Angelogianni, 1989; Gianoulakis et al., 1987, 1996; Thiagarajan et al., 1989) as well as in cell cultures of rat hypothalamus and pituitary (Gianoulakis and Barcombe, 1987; Gianoulakis et al., 1990; Keith et al., 1986). More recently, animal studies have also demonstrated that alcohol exposure also increases levels of another class of opioid peptides, the metenkephalins. Moreover, studies using rodents bred specifically for preference or nonpreference for alcohol and in humans with a positive or negative family history of alcoholism indicate that a genetic predisposition toward alcohol consumption is accompanied by alterations in the responsiveness of the endogenous opioid system (deWaele et al., 1992). Acute alcohol administration produces greater increases in release of endogenous opioids and larger increases in opioid peptide gene expression in alcohol-prefering rodents than in nonpreferring rodents (Froehlich, 1995; Froehlich and Wand, 1996). Acute alcohol administration has also been shown to increase endorphin and enkephalin gene expression and to increase opioid receptors in neuronal cell cultures (Charness et al., 1986, 1993; Jenab and Inturrisi, 1994; Li et al., 1996). Recently, Gianoulakis and colleagues found that individuals with a positive family history of alcoholism have lower baseline levels of beta-endorphins than individuals with no family history of alcoholism (Gianoulakis et al., 1996).

**Effects of Exogenous Opiate Administration and Withdrawal on Alcohol Consumption**

A related line of research has explored the impact of exogenous opiates on alcohol consumption in animal models. Early studies found that rats injected with a single, high dose of morphine (30 mg/kg) decreased their
alcohol consumption (Sinclair, 1974) and that this effect of morphine was dose dependent (Ho et al., 1976). These studies also reported that morphine administration did not alter water consumption, suggesting a selective effect of morphine on alcohol-drinking behavior (Sinclair, 1974). Self-administration of alcohol also increased if moderate to large doses of opioids were abruptly terminated and withdrawal symptoms precipitated (Volpicelli et al., 1991; O'Brien et al., 1996).

In contrast to these earlier findings, Reid and colleagues found that small doses of morphine (<2.5 mg/kg) transiently increased the preference for alcohol in previously fluid-deprived rats when given limited (2-hour) access to alcohol or water immediately after injection (Reid et al., 1991). These results suggested that small doses of opiates or other pleasure-inducing drugs may have a priming effect in which small amounts of the rewarding substance increase the craving to consume more of the same substance. In contrast, if opioid receptors are already saturated by high levels of externally administered opioid agonists such as morphine or heroin, then drinking decreases.

Similarly, an addictive cycle (Figure 3-4) may be established in animals or humans as a result of consuming a small dose of alcohol, which like a small dose of morphine leads to modest increases in opioid receptor activity. Once opioid receptor activity has been primed, more alcohol is needed to ensure continued opioid receptor activity (Volpicelli et al., 1994). Therefore, a cycle may ensue during which the desire to increase or recapture feelings of pleasure or euphoria (particularly if withdrawal results in lower levels of the desired feeling) is translated into cravings for particular substances. The loss of control that follows the initial consumption of a reinforcing agent may provide the root mechanism for some, if not all, addictive behaviors.

**Effects of Opioid Antagonists on Alcohol Consumption**

Nonselective opioid antagonists like naloxone and naltrexone block opioid receptors and reverse the effects of endogenous opioid peptides as well as exogenous opiates (Froehlich, 1995; Swift, 1995). Studies conducted in both rodents and monkeys have demonstrated that naloxone and the longer acting naltrexone attenuate voluntary self-administration of alcohol and stress-induced increases in alcohol consumption, suggesting that these agents may prevent the reinforcing effects of alcohol consumption (Froehlich and Li, 1993; O'Brien et al., 1996).

Pretreatment with opioid antagonists reverses most of the effects of endogenous opioids or exogenous opiates on alcohol preference. Two double-blind, placebo-controlled clinical trials on the effects of naltrexone on alcohol drinking in outpatient alcohol-dependent patients demonstrated that naltrexone can decrease the mean number of drinking days per week, the frequency of relapse, the alcohol-induced subjective "high," and the desire to drink (O'Malley et al., 1992; Volpicelli et al., 1992).
Boxes

- Opiates such as morphine and heroin are derived from opium, which is harvested from the opium poppy (*Papaver somiferum*). Through their research on opiate addiction, scientists discovered specific sites in the central nervous system where opiates attach and exert their effect. These sites are called opioid receptors. Subsequent to this discovery, scientists were able to identify the naturally occurring chemicals produced by the body that also attach to opioid receptors.

- In this document, the term *opiate* refers to drugs like morphine and heroin, whereas the term *opioid* refers to naturally occurring chemicals such as enkephalins and endorphins (endogenous opioids) that exert opiate-like effects by interacting with central nervous system opioid receptors.