Keynote Address: Neurobiological Correlates of the Addictions: Findings From Basic and Treatment Research

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INTRODUCTION

This chapter summarizes some aspects of what is known about the neurobiological correlates of the addictions from basic and treatment research. Issues of known differences between males and females are discussed as well as areas of no known differences. Frequently, it is not known whether differences exist or which areas require special attention to women and sex differences, because of biological, behavioral, social, or environmental issues.

There are about 54 million regular smokers of cigarettes in the United States, and increasingly, these are young women. There are more than 10 million—perhaps as many as 15 million—alcoholics, and a large portion are women. More than 23 million persons in the United States have used cocaine at some time, and approximately 1 million are regular users of or are addicted to cocaine. It has been estimated that 2.7 million persons in the United States have used heroin at some time, and approximately 1 million are addicted to heroin by the definition of Federal guidelines (Kreek 1987, pp. 1597-1604; Kreek 1991, pp. 245-266; Kreek 1992*a*, pp. 205-230; Kreek 1992*b*, pp. 255-272; Kreek 1992*c*, pp. 997-1009). Operationally, and to meet criteria for admitting people into treatment with methadone or l-alpha-acetyl-methadol (LAAM), heroin addiction is defined as self-administration of multiple daily doses of heroin for 1 year or more, with the development of tolerance, physical dependence, and drug-seeking behavior. Various studies have estimated that 30 to 50 percent of each of these groups who abuse drugs and are addicted are women (Finnegan et al., 1995, pp. 45-48).

Since 1969 the Laboratory of the Biology of Addictive Diseases at Rockefeller University has collected and frozen blood specimens prospectively from various studies, including basic and treatment

research. In 1983 these specimens were unbanked and uncoded, with the exception of indicators of drug abuse history and demography. Subsequent testing of these blood specimens for human immunodeficiency virus-1 (HIV-1) antibodies, using the increasingly precise and sensitive tests developed by the Centers for Disease Control and Prevention, indicated that HIV-1 entered the drug-abusing population in 1978 and that the prevalence rapidly ascended until it peaked and plateaued in 1983, with 50 to 60 percent of all street addicts being HIV-1 infected by that time. In New York City, the epidemic of HIV-1 infection reached parenteral drug abusers in 1978 (Des Jarlais et al. 1984, 1989; Novick et al. 1986*a*, pp. 318-320; Novick et al. 1986*b*; Kreek 1990, pp. 181-187). It is still spreading to various parts of this Nation and the world.

The New York City Department of Health has been tracking HIV-1 infection and acquired immunodeficiency syndrome (AIDS) according to many different parameters, including sex. Its most recent data on AIDS cases among women show that major risk groups for HIV-1 infection in women are intravenous drug users and heterosexual nonusers of drugs who develop HIV-1 infection and AIDS through contact with male drug users. Among women of reproductive age in New York City, AIDS is now the leading cause of death. The concordance of HIV-1 infection and drug abuse, coupled with the rapid rise of HIV-1 infection in women, makes it imperative to stop denial and begin to address the drug abuse problems of women at the levels of prevention, early intervention, treatment, and research.

VULNERABILITY AND NEUROBIOLOGICAL BASIS OF ADDICTION

The author's laboratory at Rockefeller University focuses on directly or indirectly addressing issues related to elucidating the vulnerability and neurobiological basis of addiction. Genetic factors are suspected to play a role in the development of addiction in some persons. In addictive diseases, as well as in many other behavioral and physiological diseases, there probably are multiple genes involved. There may be several normal (or mutant) alleles, that is, variations at specific loci in specific genes, that individually may confer no danger or hazard but that in combination may confer a vulnerability for development of an addiction. However, it is a vulnerability only because exposure to another

drug or alcohol must follow. That is when prevention and early intervention efforts become so important.

Increasing data unequivocally demonstrate that drugs of abuse alter normal physiology in distinct and definable ways (Kreek 1987, pp. 1597-1604; Kreek 1991, pp. 245-266; Kreek 1992*a*, pp. 205-230; Kreek 1973*a*, 1978; Novick et al. 1989, 1993). These alterations include changes in normal stress response, reproductive biology, and immune function. Each one of these perturbations may contribute to an addictive disease or to some of the health consequences of addictions. The changes may be persistent or permanent.

There also are variable host responses to drug exposure that may be caused in part by altered or different physiological and pathological states, developmental or environmental factors, adolescence, or pregnancy. Clearly, this is a gender issue. Chronic diseases and responses to stressors all may play a role.

ROLE OF ENDORPHINS

Many laboratories have questioned the role of the endorphins or the endogenous opioid system in each of three major addictions: heroin addiction, cocaine dependence or addiction, and alcoholism. It has been known for more than a decade that this important physiologic system, the endogenous opioid system, is involved in several aspects of normal physiology, including stress responses, reproductive biology, and immune function, as well as gastrointestinal function, cardiovascular status, and many behaviors, probably including mood changes and response to pain. There are three classes of endorphins: beta endorphins (derived from the proopiomelanocortin [POMC] gene), enkephalins, and dynorphins.

Following the 1973 elucidation of opiate receptor existence by Snyder, Simon, and Terenius of Johns Hopkins University, New York University, and Uppsala University, respectively, the first of these three classes (the enkephalins) was found by a group in Aberdeen, Scotland, consisting of Kosterlitz and Hughes in 1975; subsequently, many others went on to define biochemically and clone single genes for each of the three opioid classes (Pert and Snyder 1973; Simon et al. 1973; Terenius 1973; Hughes et al. 1975). Each of these genes (proopiomelanocortin, proenkephalin, and prodynorphin) yields a single-gene product.

Using increasingly selective synthetic ligands (i.e., chemicals that bind to the opiate receptors), by the late 1980s three separate types of opiate receptors had been clearly defined: mu, delta, and kappa, possibly with subtypes. In December 1992 the first opiate receptor was successfully cloned. The delta opiate receptor was first independently cloned by two groups of scientists, Evans and colleagues at the University of California at Los Angeles and Kieffer and colleagues in Strasbourg, France, using new techniques that had been developed over the preceding years (Evans et al. 1992; Kieffer et al. 1992). Shortly after the original cloning, these and other groups—NIDA, including Uhl of the Division of Intramural Research (DIR); the groups of Yu at the University of Indiana, Reisine at the University of Pennsylvania, and Bell at the University of Chicago; and Akil, Watson, and Thompson at the University of Michigan—cloned the mu and kappa opioid receptors (Wang et al. 1993, 1994; Chen et al. 1993*a*, 1993*b*; Raynor et al. 1994; Thompson et al. 1993). The original cloning was from mouse and rat; subsequent cloning of human genes has been achieved.

A portion of the opioid receptor is outside the cell wall, with an N terminal region plus three extracellular loops, to which heroin, morphine, and similar drugs, as well as the endogenous opioids—endorphins, enkephalins, and dynorphins—bind. The message is transduced, and the signal is amplified from the carboxy terminus and intracellular loops part of the molecule. Many laboratories, including the author's, are interested in the 5' (upstream) regions of these genes because that is where gene expression is controlled. The 5' region controls how much mRNA will be formed and, thus, how much peptide may be produced. That region contains many different zones; two of them are of special interest for this discussion (Wang et al. 1993, 1994; Chen et al. 1993*a*, 1993*b*; Raynor et al. 1994; Thompson et al. 1993).

One zone is a site where the stress-responsive glucocorticoid steroids, like cortisol in humans (or corticosterone in rats), may act to change gene expression; this particular glucocorticoid response element (GRE) region is also found upstream of many other genes, including genes for the endogenous opioid peptides. There also are regions on the 5' areas of many genes where progesterone and estrogens may act. One fundamental question is whether gene expression of specific opioid peptides and receptors is different in females, with more estrogen and progestins, from that in males.

A technique modified at the author's Laboratory of the Biology of Addictive Diseases and at DIR is used to measure how much message of each gene of the endogenous opioid system is expressed, first carrying out studies using a rodent model, primarily in rats (Branch et al. 1992; Spangler et al. 1993*a*, p. 142; Spangler et al. 1993*b*; Unterwald et al. 1995; Spangler et al. 1996*a*, 1996*b*; Chou et al. 1993*a*). This technique is being used to map where the opioid genes are expressed in different brain regions. Abundant expression of preprodynorphin and proenkephalin genes occur in two regions, the nucleus accumbens and the caudate putamen. These regions are part of the mesolimbic, mesocortical, and nigrostriatal dopaminergic pathways, which are known to be central sites of action of drugs of abuse. They are sites where reinforcing effects, locomotor effects, and some other important effects of drugs of abuse occur. Abundant expression of these genes also is found in the hypothalamus, an area where neuroendocrine control of both the stress response and reproductive biology occurs.

Recently, several laboratories obtained cDNA probes of the opioid receptor genes from the researchers who did the original cloning. After subcloning these probes to make proper riboprobes, the author and others are beginning to map where the specific opioid receptor genes are expressed. The mu opioid receptor is abundant in the regions where drugs of abuse are known to act, as well as in the hypothalamus, where there is neuroendocrine control of many functions, and in the thalamus, a site important for the expression of pain. Similarly, the kappa opioid receptor is abundant in these same regions involved in drug abuse, addictive diseases, and neuroendocrine functions.

Laboratories are not restricted to studies in rodents; because of the development of exciting technologies in imaging, the human brain can now be imaged (Kling et al. 1997, p. 120). Cyclofoxy, a compound synthesized by Rice at the National Institutes of Health (NIH), is an opioid antagonist that, when injected into a normal volunteer in a radioisotope-labeled form, binds to and allows visual imaging of many specific opioid-receptor-containing regions of the brain. This radioactive ligand binds very selectively in humans in the same regions that have mu and kappa opioid receptors in rodents—the thalamus, amygdala, anterior cingulate, caudate, and putamen (including nucleus accumbens parts of the striatum) as well as in the hypothalamus (Kling

et al. 1997, p. 120). Thus, for the first time, it is possible to conduct studies in both normal volunteers and humans suffering from addictive diseases and ask questions about where the opioid receptors are, how they are affected by drugs of abuse, and whether there are gender differences in these opioid receptor systems (Kling et al. 1997, p. 120).

PHARMACOTHERAPY OF HEROIN ADDICTION

In 1964 the author took a research elective that became a research effort of more than 30 years at Rockefeller University, by joining Dole and Nyswander in the initial work to attempt to develop a new long-term approach for managing heroin addiction. At that time, Dole had recognized from serving on the Working Group on Narcotic Addiction of the Health Research Council of the City of New York that heroin addiction was the number one problem causing, or contributing to, many infectious disease problems, in addition to its own devastating effects as a disease (Kreek 1987, pp. 1597-1604; Kreek 1991, pp. 245-266; Kreek 1992*a*, pp. 205-230; Kreek 1992*b*, pp. 255-272; Kreek 1992*c*, pp. 997-1009; Dole et al. 1966). The best drug-free approaches were successful in reaching only a small percentage of persons, and of those who had access to such treatment, only 15 to 30 percent were able to stay abstinent from opiate drugs for 1 year or more. That 15- to 30-percent maximum has been replicated worldwide, even in the most recent studies, with respect to attempts to treat "hardcore," long-term, 1-year-or-more opiate-dependent persons in a medication-free approach.

Therefore, the author and colleagues began to articulate goals, develop a rationale, and develop a specific pharmacotherapy for opiate or any other addiction (Kreek 1992*a*, pp. 205-230). First, one must try to prevent withdrawal symptoms, if they exist, and they do exist with opiate dependence; second, to reduce drug craving for each of the addictions; third, to normalize any physiologic functions disrupted by drug abuse; and finally, drawing in the need for specific research, to target the treatment agent to specific sites of action, receptors, or physiologic systems that have been affected or deranged by the drug of abuse.

A person addicted to heroin injects the drug three to six times each day, initially to achieve a euphoric "high" state. With the development of tolerance—that is, the cellular and biochemical adaptation that makes an addicted person or a pain patient need increasing amounts

of the drug (in the case of the addicted person, to achieve a high, or in the case of a pain patient, to get relief from pain and to prevent withdrawal symptoms)—increasing amounts of opiate must be used. If a drug is not used, withdrawal symptoms will ensue.

Investigators realized that a medication to manage addiction, in addition to achieving the articulated goals, would have to be orally effective to get an addicted person away from the street lore, habits, and dangers of unsterile needle use; it also would have to be long-acting. As of 1964 there were no good analytical chemical methods that would allow the measurement of blood levels of morphine or any other opiate drug, including the synthetic but potentially effective oral medication methadone.

Methadone had been studied at a limited number of sites for possible use in pain management (Kreek 1996, pp. 487-541). It also had been studied in New York and at the Lexington, KY, Public Health Service facility for possible use in detoxification management of addiction (Kreek 1996, pp. 487-541). Early studies showed that methadone is effective when given orally and that it has an onset of action within 30 minutes and a duration of action of 24 to 36 hours, much longer than the 3- to 6-hour duration of heroin's action. Those studies also showed that if a dose is properly selected—and this is critical—to be less than that to which tolerance has developed in each individual, no euphoria or other narcotic signs or symptoms, especially sleepiness, would ensue. It was found that methadone would protect against the onset of withdrawal symptoms for 24 hours (Kreek 1991, pp. 245-266; Kreek 1992*a*, pp. 205-230; Kreek 1992*b*, pp. 255-272; Kreek 1992*c*, pp. 997-1009; Dole et al. 1966). A single daily oral dose placed a person formerly addicted into a normal, or "straight," physiologic and behavioral state, but if no medication were given after 24 hours, withdrawal symptoms or "sickness" would ensue.

A series of double-blind studies then was conducted for two purposes: (1) to address the question of whether harm would result if a former addict, treated with methadone, superimposed an illegal dose of heroin and (2) to address the mechanism of action of methadone. Two 4-week, double-blind, random-order studies were conducted. It was found that no narcotic-like effect could be appreciated when doses of heroin, then costing up to $200, were administered against a background treatment dose of 60 mg to 100 mg of methadone a day (Dole et al.

1966). Also, no adverse effects—no respiratory depression or other effects—ensued. The mechanism of action of chronic methadone treatment was elucidated; tolerance to the opioid methadone conferred cross-tolerance to any effects of the superimposed short-acting opiate heroin.

Several years later, sensitive and specific techniques were developed to measure the levels of methadone in plasma, which indicated that methadone has a slow onset of action, with a peak within 2 to 4 hours, and that the peak plasma level is barely a doubling of the steady state or nadir level (Kreek 1996, pp. 487-541; Kreek 1973*b*; Kreek et al. 1976*a*, 1976*b*; Hachey et al. 1977; Rubenstein et al. 1978; Kreek et al. 1979; Kreek 1979; Kreek et al. 1980*a*, 1980*b*; Tong et al. 1980; Kreek et al. 1980*c*; Tong et al. 1981; Novick et al. 1981; Nakamura et al. 1982; Kreek et al. 1983*a*). This is a pharmacokinetic profile different from that of heroin or morphine, each of which has a rapid and high peak plasma level, followed at once by a rapid decline. Thus, an addicted person would need to readminister the short-acting narcotic three to six times each day to prevent the onset of withdrawal symptoms. Heroin has a half-life of 2 to 3 minutes, its monoacetyl metabolite about 30 minutes, and its final metabolite morphine about 2 hours, with some effectiveness for 4 to 6 hours, whereas methadone has a half-life of 24 hours, with 48 hours for the active enantiomer (i.e., its chemically active half) (Kreek 1996, pp. 487-541; Kreek 1973*b*; Kreek et al. 1976*a*, 1976*b*; Hachey et al. 1977; Rubenstein et al. 1978; Kreek et al. 1979; Kreek 1979; Kreek et al. 1980*a*, 1980*b*; Tong et al. 1980; Kreek et al. 1980*c*; Tong et al. 1981; Novick et al. 1981; Nakamura et al. 1982; Kreek et al. 1983*a*).

The tolerance and cross-tolerance provided by chronic methadone treatment are critical not only to prevent any adverse effects but also to contribute to the effectiveness of methadone through the mechanism of extinction. Studies related to classical conditioning phenomena have taught that if no euphoria or other desired effect results from use of a drug, then ultimately, in theory at least, a person will stop administering that drug. Although classical conditioning extinction techniques have not been effective when used alone in treating addiction, methadone provides cross-tolerance to other opiate effects and a classical conditioning extinction effect, prevents withdrawal

symptoms, and allows normalization of disrupted physiology; most important, chronic methadone treatment prevents drug hunger.

Currently, there are approximately 115,000 people in methadone treatment in the United States. In good treatment programs, voluntary retention ranges from 70 to 85 percent, and continuing use of illicit heroin drops to less than 15 to 20 percent after stabilization for 6 to 12 months in treatment (Kreek 1991, pp. 245-266; Rettig and Yarmolinsky 1994). However, good programs are few because of the decrease in funding that has occurred over the past 20 years. The adjusted "real dollar" unit expenses allowed in the mid-1990s are much less than they were in the early 1970s for each formerly heroin-addicted person in a methadone maintenance treatment program; therefore, the ability of those programs to offer essential counseling services as well as access to health care, including medical and psychiatric care as needed (Blumenthal, this volume), is markedly curtailed. These reductions in available funds have caused many programs to be simply pharmacologic programs, with medication and nothing else given. Also, staff members are less well trained and less plentiful.

Comparisons of health care costs found that a good or excellent methadone program would cost less than the amount recently estimated for the average American to have overall health care. Good-to-excellent treatment programs could combine drug abuse services with all counseling and health care services for about $6,000 to $8,000 a year, more than the current $1,500 to $3,500 a year per person being given for any pharmacotherapy, and yet infinitely less than the cost of AIDS, $100,000 a year per person in the last 2 years of the life of a person who is dying of AIDS; crime on the streets, approximately $100,000 to $200,000 a year per person; or incarceration, $30,000 to $60,000 a year per person.

The author's 1984 study showed that, at a time when 50 to 60 percent of untreated homeless people with addictions were positive for HIV antibodies, of the people addicted to heroin who had the good fortune to enter an effective methadone program prior to the AIDS epidemic reaching New York City in 1978 and who remained in treatment, only 9 percent were positive for HIV antibodies, and those were patients who continued to inject cocaine (Des Jarlais et al. 1984; Novick et al. 1986*a*, pp. 318-320; Novick et al. 1986*b*).

This finding of a highly significant reduction in HIV infection has been replicated by many studies in the United States, and one by Blix (1988) in Sweden. But it has been more than 10 years since the study by Des Jarlais and associates (1984); learning must continue.

Some issues of perturbation of physiology during cycles of heroin addiction that disrupt normal life and normal physiology may contribute to the addiction pattern per se and clearly have special implications for women in the areas of stress responsivity, prolactin response, and gonadal function with related behaviors.

SIMILARITIES AND DIFFERENCES BETWEEN HUMAN AND RODENT STUDIES

Although human models are different from rodent models in some specific aspects of neurobiology and pharmacology, rodent models are essential for biomedical research. A great effort is appropriately spent studying rodents as well as other species. However, the first two items to be addressed here (pharmacokinetics and neuroendocrine effects) would not have been discovered if basic clinical research had not been carried out in humans; the effects of acute opiate, morphine, or heroin administration are different for these two indices in humans and in rats.

In humans, an acute injection of morphine to a healthy preoperative or preprocedure volunteer causes a reduction in plasma levels of the important stress responsive adrenocorticotropic hormone (ACTH), as well as beta endorphin, one of the endogenous opioids that comes from the same gene and gene product. In turn, in humans there is reduced release of cortisol, the critically important glucocorticoid, from the adrenal cortex.

It is of great importance for men and women, although with different implications, that acutely administered opiates cause inhibition of release of luteinizing hormone (LH), important for controlling levels of testosterone in males and essential for controlling ovulation and thus fertility in females. Also, acutely administered opiates cause increased release of vasopressin. Of special importance to women, the opiates also cause increased release of prolactin, which modulates lactation as well as specific aspects of immune function.

The opioid generating gene, the POMC gene, gives rise to equal amounts of ACTH and beta endorphin. These are released from the

anterior pituitary into circulating peripheral blood; ACTH acts on the adrenal cortex to cause release of cortisol, which in turn acts in a negative feedback mode at the hypothalamus to decrease production and release of corticotropin releasing factor (CRF); CRF is an important peptide that in most mammals drives the anterior pituitary to produce and release POMC and thus the peptides ACTH and beta endorphin. Cortisol also acts directly in a negative feedback mode at the anterior pituitary site to attenuate POMC synthesis, and processing and the release of ACTH and beta endorphin.

Studies have been conducted to determine how use of opiates may perturb this hypothalamic-pituitary-adrenal (HPA) system. Studies also have been conducted to determine the effects of chronic use of the short-acting opiate heroin on the important stress-response axis and to examine the effects of the long-acting opioid methadone, which has a profoundly different pharmacokinetic profile in humans (24-hour sustained action) as contrasted to a 3- to 6-hour, on-off action of heroin or morphine on the HPA function.

In animal model studies, Zhou recently readdressed the question of where a glucocorticoid like cortisol, in this case, dexamethasone, affects this important HPA axis. Dexamethasone controls CRF gene expression in the hypothalamus. Expression of the CRF gene, whose important peptide product CRF may be involved in mood, behavior, and immune function, is also present in many other regions of the brain (Zhou et al. 1996*a*, 1996*b*).

The author's group found in human studies that both acute and chronic use of short-acting opiates, such as heroin or morphine, can suppress the hormones of the HPA axis (Kreek 1973*a*, 1978; Kreek 1973*c*, pp. 85-91; Cushman and Kreek 1974, pp. 161-173; Stimmel and Kreek 1975, pp. 71-87). It was found that during steady-dose methadone treatment, this axis becomes completely normal, with normal levels and normal circadian rhythm of release of hormones from the HPA axis (Kreek 1992*a*, pp. 205-230; Kreek 1973*a*, 1978; Kreek 1973*c*, pp. 85-91; Cushman and Kreek 1974, pp. 161-173; Stimmel and Kreek 1975, pp. 71-87). However, during withdrawal from the opiates, which a person addicted to heroin experiences three to six times a day, activation of this axis is seen (Kreek 1992*a*, pp. 220-230; Kreek 1973*a*, 1978;

Stimmel and Kreek 1975, pp. 71-87; Rosen et al. 1995, 1996; Culpepper-Morgan and Kreek 1997). The addicted person experiences suppression, followed by activation of the HPA axis in a chaotic cycle.

Of great importance for research and with implications for the neurobiology of several addiction disorders such as alcoholism, it has been found that specific opioid antagonists also activate the HPA axis and thus in humans have effects opposite from the opiate agonists, which suppress this HPA axis (Kreek 1991, pp. 245-266; Culpepper-Morgan and Kreek 1997; Kreek et al. 1984*a*, pp. 845; Kreek et al. 1983*b*; Ragavan et al. 1983; Kosten et al. 1986*a*, 1986*b*; Kreek et al. 1987; Culpepper-Morgan et al. 1992; Kosten et al. 1992; Chou et al. 1993*b*). This activation may also be important in understanding why few persons addicted to heroin have been responsive to treatment with the opiate antagonist naltrexone.

The author and colleagues have studied what happens when a stress is induced by using metyrapone, which blocks cortisol synthesis and thus blocks the normal negative feedback control by glucocorticoids, both at the hypothalamic and at the anterior pituitary levels, and leads to an outpouring of CRF, beta endorphin, and ACTH (Kreek 1992*a*, pp. 205-230; Kreek 1973*a*, 1978; Kreek 1973*c*, pp. 85-91; Cushman and Kreek 1974, pp. 161-173; Kreek et al. 1981, pp. 364-366; Kreek and Hartman 1982; Kreek et al. 1983*c*, 1984*b*). In the setting of chemically induced stress, it has been found that people addicted to heroin are hyporesponsive. Conversely, persons who had been addicted to heroin who are methadone maintained become normal in their response to this stress challenge. In further studies pursuing this question, it has been found that drug-free, formerly heroin-addicted people appear to be hyperresponsive to this chemically induced stress (Kreek 1992*a*, pp. 205-230; Kreek et al. 1984*b*). It also has been found that abstinent people addicted to cocaine are hyperresponsive (Kreek 1992*a*, pp. 205-230; Kreek 1992*d*, pp. 44-48). It should be asked whether this hyperresponsivity to stress drives (medication-free or heroin-free) formerly heroin-addicted people to readminister opiates and possibly drives the cocaine-addicted person to continue to use cocaine or, more likely, opiates.

It is now known that both cortisol and the endogenous opioids are involved in the normal regulation of the HPA axis and that these opioids and their function become abnormal or disregulated in the

setting of opiate addiction and also cocaine addiction (Zhou et al. 1996*a*, 1996*b*).

ISSUES PERTINENT TO WOMEN

Prolactin is released in response to opiates in both human and rodent models. In chronic methadone treatment, studies of women have shown that their prolactin levels become normal; however, responsivity to peak levels of methadone continues to occur, as in men during chronic methadone treatment, with no full tolerance or adaptation developing (Kreek 1978). The next question addressed was whether prolactin would rise normally in pregnancy in a methadone-maintained woman, and it was found that this does happen.

It also was found that during the second half of pregnancy, when levels of the steroid progesterone are increasing dramatically, this female steroid affects hepatic drug-metabolizing enzymes and increases the liver's ability to eliminate certain medications and that methadone plasma levels become significantly lowered, even though the woman may be maintained on a steady dose of methadone (Kreek 1979; Pond et al. 1985). In one study, the same women were studied on 2 days during late pregnancy and then restudied after delivery on 2 days; after delivery, the plasma levels of methadone returned to what would be considered normal levels for the dose administered (Pond et al. 1985). Thus, one must be careful in considering any dose reduction during late pregnancy because there is a highly notable sex- and condition-specific issue of pregnancy, specifically late pregnancy, when progesterone levels become high. This problem specifically pertains to women. It is recommended that levels of methadone be maintained during the last two trimesters of pregnancy in a steady state, to prevent the onset of withdrawal symptoms.

RECENT PERTINENT RESEARCH FINDINGS

Studies have been conducted to determine whether opiate treatment with the long-acting opiate methadone has any negative effects on immune function, because many studies in animal models and some in human models suggested (and now have documented) that endogenous opiates as well as exogenous opiates may alter specific indices of immune function. This question was addressed for heroin addicts and long-term

methadone-maintained patients with similar numbers of years of exposure to various diseases through intravenous drug use, because the most common cause of abnormal immune function in an addicted individual is probably not a drug effect directly but rather the exposure to and existence of multiple chronic diseases. However, the opiate may well contribute to immune dysfunction, as it does in animal models. It has been found that, whereas heroin-addicted persons without HIV-1 infection have abnormal absolute levels of both CD-4 and CD-8 cells, which are important for the balance of immune function and become disrupted in AIDS, long-term methadone-maintained patients (in this study, a minimum of 11 consecutive years) on moderate-to-high doses of methadone have normal absolute levels of CD-4 and CD-8 cells (Novick et al. 1989). These methadone-maintained subjects, none of whom had HIV-1 infection, would have had maximum drug (opioid) effects if there were to be a deleterious effect, because methadone is an opioid, long-acting in humans compared with heroin, and administered in moderate-to-high doses for 11 or more years. It also was found that natural killer cell activity becomes normal in long-term methadone-maintained patients, whereas it is significantly lowered in active heroin-addicted people (Novick et al. 1989). There is interest in drug effects, as well as other effects, on natural killer cell activity, because natural killer cells are the first line of defense against many diseases that may play a role in the progression of HIV-1 infection to AIDS.

In the chronically methadone-maintained patient, there is also a normalization of the reproductive biological axis, as well as the stress-responsive axis, and in turn the immune function, that may be linked to the normalization of neuroendocrine function.

PROBLEMS OF COCAINE ADDICTION

It would be nice if the drug abuse story could end with heroin and its successful management (if only education and treatment resources could be made available), but cocaine abuse is also a major problem. Heroin abuse and addiction are on the ascendancy, but it is known that part of the ascendancy of the heroin epidemic now results from many who start their drug abuse history with cocaine abuse and addiction and turn to heroin use for self-medication. Increasing numbers of people now addicted to heroin began their drug abuse history with cocaine dependence.

Cocaine acts primarily to block the dopamine reuptake transporter, the presynaptic mechanism that takes dopamine from synapses back up into cells. Thus, cocaine use causes an abnormally increased amount of dopamine in the extracellular fluid of critical brain regions, the striatum and the nucleus accumbens, where the so-called rewarding effects and locomotor activity effects of drugs of abuse occur.

In studies of a rodent model, with three cocaine administrations per day, a "binge" pattern model has been found in which dopamine goes up in response to each of these three administrations, but after 3 to 5 hours, dopamine levels in extracellular fluid, as measured in microdialysis studies, are down to normal or even below normal after chronic cocaine administration (Maisonneuve and Kreek 1994; Maisonneuve et al. 1995). So what causes craving, and what is the neurobiologic basis of the persistent use of cocaine?

One suggested hypothesis is that the cause of persistent craving or drug hunger may reside in part in the endogenous opioid system. In work done by Unterwald in the author's laboratory, when this binge pattern was applied to rodents, both the mu and the kappa opioid receptors were significantly increased in density in the regions of the brain involved in the rewarding and locomotion activity effects of cocaine, specifically the caudate putamen and the nucleus accumbens (Unterwald et al. 1992, 1994*a*).

Spangler, also in the author's laboratory, has shown that dynorphin gene expression is increased in the striatum in this setting of binge pattern cocaine administration, results that have been corroborated by others using single-dose or self-administration models in subsequent studies also conducted in rodents (Spangler et al. 1993*a*, p. 142; Spangler et al. 1993*b*). The role that the dynorphin peptides play in modulating the effects of cocaine on dopaminergic surges is being questioned, with the ultimate goal of determining whether this natural endogenous opioid can be used to help decrease this excess dopamine activity (Spangler et al. 1996*a*, p. 142; Spangler et al. 1996*b*; Unterwald et al. 1994*b*; Kreek et al. 1994, p. 108).

It is not known whether this is possible, but there is one exciting new finding, which clearly is critical for females, possibly even more than for males, concerning normal physiology: Dynorphin peptides are potent modulators of prolactin release (Kreek et al. 1994, p. 108). Pilot studies have demonstrated that when dynorphin is administered to

healthy subjects, there is increased prolactin release as reflected by increased plasma levels of prolactin, which is a brisk and direct response to the dynorphin administration. Because in humans prolactin is almost exclusively under tonic inhibition by dopamine, dynorphin peptides may act by decreasing dopamine tone, thus causing increased serum prolactin levels (Kreek et al. 1994, p. 108). This finding may be important for physiology; it may also be important for understanding and perhaps managing cocaine dependence in the future (Claye et al. 1996, p. 132).

SUMMARY

The biological basis of addiction must be understood to enhance prevention, early intervention, and treatment efforts. In the author's laboratory, one area of research has been chosen, but it has been critical to combine both laboratory studies and basic clinical research studies, as well as applied treatment research studies with the author's clinical colleagues Dr. Aaron Wells and Dr. Elizabeth Khuri. This multidisciplinary approach allows for truly rapid and effective translational research between the laboratory and the clinic and vice versa to provide a better understanding of these addictive diseases and the hope of helping more men and women afflicted with these diseases.

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ACKNOWLEDGMENTS

This work was conducted with support from grants from the New York State Office of Alcoholism and Substance Abuse Services, NIDA Research Center (P50-DA05130), NIDA Research Scientific Award (K05-DA00049), and General Clinical Research Center (M01-RR00102) from the National Center for Research Resources at the National Institutes of Health.

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