Neurobiology of Addictive Behaviors and Its Relationship to Methadone Maintenance

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Abstract

Scientific information about the neurobiology of addictive behaviors provides an increasingly important rationale to support opioid agonist pharmacotherapy, primarily methadone maintenance treatment, for long-term heroin addiction. In late 1963 and 1964, the first research was performed at The Rockefeller Institute for Medical Research by Dole, Nyswander, and Kreek in an attempt to develop a new pharmacotherapy for opiate addiction. The hypothesis underlying that research was that heroin addiction was a disease. However, the evidence for heroin addiction being a disease was based primarily on clinical anecdotes and the natural history of opiate addiction. Until then chronic addiction was managed primarily using abstinence-based, medication-free behavioral approaches. Such approaches were uniformly successful in only a small percent of long-term heroin addicts. Subsequent research, both clinical research as well as laboratory-based research, using a variety of appropriate animal models as well as *in vitro* techniques, has shown that drugs of abuse in general, and specifically the short-acting opiates, such as heroin, may profoundly alter molecular and neurochemical indices, and thus physiologic functions. Also, research has shown that after chronic exposure to a short-acting opiate, these alterations may be persistent, or even permanent, and may contribute directly to the perpetuation of self-administration of opiates, and even the return to opiate use after achieving a drug-free and medication-free state. There is ample evidence now that disruption of several components of the endogenous opioid system, ranging from changes in gene expression to changes in behavior, may occur during cycles of short-acting opiate abuse. Also, there are very convincing studies that suggest that stress responsivity is profoundly altered by chronic abuse of short-acting opiates including: documentation of atypical hypo-responsivity to stressors during cycles of heroin addiction; evidence of sustained hyper-responsivity to stressors in the medication-free, illicit-opiate-free state; and in contrast, normalization of stress responsivity, as reflected by the hypothalamic-pituitary-adrenal axis function in long-term, methadone-maintained patients. Thus, both laboratory and clinical research studies provide firm documentation that the disruption of physiologic, as well as behavioral, functions occurs during chronic administration of short-acting opiates. Also, there is research evidence of an epidemiologic, and more recently of a molecular genetics type, that a genetic vulnerability to develop addictions in general, and opiate addiction specifically, may exist, and that early environmental factors may alter physiology to enhance vulnerability to develop opiate addiction when self-exposed.

Key Words: Heroin, methadone, heroin addiction, methadone maintenance, neurobiology of addiction.

THE INAPPROPRIATE USE of mood-altering drugs transcends the medical arena, and the health costs associated with such use are enormous. Most important, it is the physician who is often the first person to have an opportunity to identify individuals who either have the potential to become drug-dependent or are currently using mood-altering substances. Unfortunately, the conclusion often made by those devoted to the study of addictive behaviors is that physicians, who have been trained to be critical thinkers, lose this ability when dealing with patients who are addicted. Too many physicians share the perception that drug dependence, once developed, is primarily a character defect associated with criminal behavior, which might be best managed outside of the medical realm. In short, drug dependency is often perceived as a socioeconomic or psychosocial, rather than a medical, problem.

There is no question that the sociological, economic, and psychological factors leading to inappropriate use of mood-altering drugs are exceptionally important, as is the need for increased funding to prevent such use. However, recent evidence unequivocally establishes the existence of neurobiological determinants of both initial and especially continuing drug use. The initiation of drug use is a voluntary, self-willed action. Nonetheless, once this use continues, depending on the specific drug, considerable change occurs in the brain that, unless understood and addressed, makes it quite difficult, though obviously not impossible, to provide effective treatment.

As noted by Gardner (1), with the exception of hallucinogens, laboratory animals will voluntarily self-administer mood-altering substances commonly used inappropriately by humans. In addition, with respect to such drugs as cocaine,

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animals will continue to administer these substances, often choosing them over food and water. Although there are distinct differences between euphoria- and/or dependence-producing drugs (Table 1), with the inability of drugs within one group to adequately relieve withdrawal or "craving" for drugs in other groups, all of these agents have one thing in common: they enhance the activity of specific neurobiological circuits. These circuits are commonly described as the "brain reward system."

It is generally believed that the more efficacious the drug is at rapidly producing its pharmacological actions at these sites, the greater its potential for addiction. The actual molecular sites of action of many of these drugs have been well categorized. Through imaging, microdialysis and quantitative autoradiography, as well as other techniques, including genetic cloning, many of these initial sites of drug action have been well established, as have the involved neurotransmitters, or neuropeptides. The effects of these substances of abuse on the reward system of the brain have been able to explain, in part: the clinical phenomena of the pleasure often associated with use of these drugs; the persistent craving that causes the chronic drug user to continue taking the drug; and some of the reasons for both early and late physiological syndromes of withdrawal when specific drugs, such as opiates or alcohol, are abruptly discontinued (Table 2).

TABLE 1
Dependence-Producing Drugs

Group	Examples
Alcohol — Sedatives — Hypnotics — Minor Tranquilizers	Alcohol, barbiturates, chloral hydrate, meprobamate, benzodiazepines
Hallucinogens	Lysergic acid and hallucinogenic amphetamines, mescaline, peyote, khat
Marijuana	Marijuana
Opiates and Opioids	Agonists: morphine, opium, heroin, codeine, meperidine, methadone Partial agonist: buprenorphine Agonist-antagonists: butorphanol tartrate, pentazocine
Stimulants	Amphetamines, cocaine, methylphenidate, weight-reducing drugs
Volatile Solvents	Glues, some cleaning fluids

TABLE 2
Why People Use Mood-Altering Drugs

Reason	Site
Euphoria (Pleasure)	Nucleus accumbens (NAc) Ventral tegmental area (VTA)
Fear of Withdrawal	Locus ceruleus
Drug Craving	Multiple brain sites

Neurotransmitters and Opioid Receptors

The most prominent neurotransmitters and neuropeptides in this process are dopamine, serotonin, glutamate, gamma-aminobutyric acid, and the endorphins (or endogenous opioids) (2–4). Dopamine is credited with playing the primary role in producing most of the euphoria seen with cocaine, nicotine, alcohol, and other stimulants, and is known to contribute to the positive reinforcing effects of heroin and other opiates (4–6). The intensity of euphoria expressed with cocaine has been shown in one study to be proportional to the percentage of dopamine transporters blocked by the drug (7). Rapidly decreasing levels of dopamine following stimulant use are also believed to be responsible for the "crash" observed in outpatient, but not in stress-minimized, inpatient settings when these drugs are discontinued. Very recently, studies were conducted in a molecularly altered "transgenic" mouse model in which the dopamine transporter gene had been deleted (a "knock-out" model). A situation was thus created in which cocaine could not cause increases in extracellular fluid levels of dopamine by blocking the transporter; this in turn removed the putative "rewarding" effect of dopamine surges. These animals were found to self-administer cocaine as readily as the "wild type" mice with intact dopamine transporters (8).

One major type of opioid receptor, namely the mu receptors, has been shown to be responsible for the primary action, including the euphoria experienced by many, but not all, when opioids such as heroin are self-administered. Correspondingly, it is felt that the kappa opioid receptor is responsible for dysphoria, rather than euphoria, and may play a role in opioid withdrawal, although recent studies have shown that natural kappa receptor-directed ligands, the dynorphins, do not cause dysphoria and may augment, not oppose, mu receptor-directed events (9–11). Endorphins, dynorphins, and enkephalins, in

response to other drugs such as alcohol and stimulants, are believed to play a role in drug-rewarding effects and also dependence, including alcohol dependence, when this occurs. This phenomenon may explain the observed benefit of naltrexone in decreasing the craving for alcohol.

Cells in the locus ceruleus that secrete norepinephrine have been demonstrated to be responsible for part of the withdrawal phenomena seen with sudden discontinuation of opioids, which results in an outpouring of norepinephrine. However, this "noradrenergic cascade" does not explain many of the acute and subacute phenomena of withdrawal, or any of the signs and symptoms of protracted abstinences. Similarly, serotonin (5-HT) has been related not only to impulsiveness and appetite, but also to dependence and craving. With respect to signal transduction, while opiates acutely inhibit the cyclic adenosine 3'5' monophosphate (cAMP) pathway at time of administration, chronic use results in an upregulation of the cAMP pathway. Abrupt cessation of opiate use leaves an upregulated, unopposed pathway, which in the locus ceruleus results in an increased firing of these cells, and withdrawal (4, 12). There is no question that as neuroscience continues to advance, additional neurotransmitters and receptor sites will be identified, and the understanding of molecular and cellular bases of addiction will become increasingly clear.

The Role of Pharmacokinetics

Parallel to the advances in neurobiology, continued work on the pharmacokinetics of drugs of abuse has helped explain the clinical phenomenon with respect to choice of drugs of abuse. As reviewed by Nutt and Uhl et al. (3, 5), the goal of the drug user is to increase the rate of delivery of the drug to the brain. This explains why a heroin user may progress from smoking heroin, to snorting and then to injecting heroin intravenously. Similarly, cocaine use provides little immediate effect when coca leaves are chewed, but considerable euphoria when freebase "crack" cocaine is smoked or when cocaine is injected intravenously. An understanding of the pharmacokinetics of the euphoria produced by such drugs, especially heroin, which have a very rapid onset and short duration of action, becomes essential when discussing the concept of maintenance for opioid dependency and in understanding the appropriate drugs to use in the pharmacologic therapy for the addictions (13). For example, a drug such as methadone has a very slow onset and long duration of action. It thus occupies the opioid receptors

much more slowly than does heroin, and it also provides a sustained perfusion of agonist, allowing the brain to compensate for the deleterious effects of the short-acting, rapid onset and offset of heroin, and it does so without producing euphoria.

The Tolerance Threshold

Equally important is an understanding of the clinical phenomena of euphoria, tolerance, and withdrawal with respect to the opioids. It has been demonstrated repeatedly that an individual dependent on an opioid to which he/she has become tolerant has developed a tolerance threshold that, if exceeded too rapidly or too far, can produce euphoria and, if very rapidly and very far, an overdose. Correspondingly, if this tolerance threshold is diminished too rapidly, withdrawal can occur.

However, when an individual is at his/her tolerance threshold to an opioid, normal cognitive and motor functions are maintained and, unless an opioid antagonist is administered to produce withdrawal, it is quite difficult, if not impossible, to determine that the individual is taking an opioid (14–16). This phenomenon explains why individuals with chronic pain syndromes who are maintained on opioids at just above the tolerance threshold, and at a level that relieves the pain but does not cause euphoria, function quite normally, and why individuals on long-acting opioid agonist maintenance therapy for opiate (primarily heroin) addiction with an appropriate agent (e.g., methadone or l-alpha-acetylmethadol) can lead productive and fruitful lives without any long-term risks from such therapy. Failure to understand this not only has resulted in the concept of maintenance therapy being derided and often rejected by those in the health professions but, equally important, it has resulted in patients in chronic pain suffering needlessly.

Heroin Addiction

Keeping this in mind, it is now appropriate to review the course of addiction of a person who becomes dependent on heroin. Since heroin is a relatively short-acting drug and the initial goal is to achieve euphoria, it is necessary to inject the drug several times a day. Each time the drug is injected, the heroin rapidly occupies the opiate receptors and produces its effects. However, with repeated injections, tolerance does develop. Since the goal is euphoria (a "high"), the individual self-administers a progressively larger quantity of heroin. As a result, the heroin user is rarely normal (in a "straight state") either physio-

logically or behaviorally. Dole et al. (14), describe the user as euphoric when "high." This state is followed by sedation and withdrawal signs and symptoms which render the individual incapable of functioning. When the "high" dissipates and the heroin level starts to drop below the tolerance threshold, withdrawal develops, associated with a "drug craving" to relieve the symptoms of anxiety, tremors, perspiration, muscle and bone pains, and nausea that comprise withdrawal. Drug craving also persists long after the acute withdrawal symptoms have dissipated in persons who attempt abrupt discontinuation of use. In fact, such drug hunger persists in persons after detoxification, regardless of the technique used (16).

It can therefore be seen that chronic use of short-acting opioids such as heroin is responsible for alterations of neurobiological systems, which in turn are responsible for both euphoria and withdrawal symptoms (13, 14). It has been demonstrated by Kreek (15, 16) that such alterations persist even following complete withdrawal of the opioid, clinically manifested by the persistent drug craving considered responsible for the high relapse rate seen in individuals who have been detoxified from heroin (15, 16). This observation has led to the hypothesis that these alterations in neurobiology and physiology, caused by chronic, long-term use of a short-acting opioid drug, may result in persistent craving and drug-seeking behavior (15, 16). In no way does this hypothesis negate the beneficial effects that may accrue from social rehabilitation, psychological counseling, and behavioral modification; rather it supports the now proven therapeutic approaches combining appropriate pharmacotherapy, using a mu opioid receptor agonist, along with counseling, and behavioral and other medical care as needed. This hypothesis also does not address the question as to why a person would initiate heroin use in the first place, although a preexisting vulnerability to develop addiction after self-exposure may exist due to genetic and environmental factors. However, it does explain why in many individuals, such rehabilitative efforts without concomitant pharmacotherapy, although their efforts are quite appropriate and intensive, may not be sufficient to maintain a state of abstinence from illicit use of drugs.

Indeed, in a laboratory model, it has been shown that withdrawal symptoms can be produced in an animal following exposure to a conditioned stimulus, if it had been previously dependent upon opioids, but maintained in a drug-free state for months; when the animal had been dependent on opioids and was given an antagonist drug, the same situation produced withdrawal (17). The human correlate of this is the former heroin addict, drug free for a long period, suddenly feeling a craving to inject heroin when entering an environment where he/she had previously taken heroin.

Maintenance Therapy

If one accepts the neurobiological explanations for drug dependence, as well as the observation that persistent neurobiological abnormalities can be demonstrated after the drug has been discontinued, one can then see why opioid agonist maintenance therapy becomes an effective approach to addressing heroin addiction. It should be emphasized, however, that maintenance therapy does not have to, nor should it, be used to the exclusion of other forms of support, including counseling, education, training and, perhaps most important, developing an understanding as to why drug use was initiated to begin with. All of these forms of support complement maintenance and should be pursued simultaneously.

In a review of the objectives of opioid agonist maintenance therapy (Table 3), the obvious immediately comes to mind. Drug craving should be eliminated, opioid withdrawal should not occur, and normal physiologic functions should be restored. However, unless continuing or recurrent heroin use can be prevented, maintenance therapy will be of little value. Prevention of heroin use is accomplished through maintaining a tolerance threshold sufficiently high to prevent euphoria from occurring, even if heroin is injected, through the mechanism of tolerance and cross-tolerance (14).

In identifying a specific agent for maintenance therapy of heroin addiction, certain charac-

TABLE 3
Objectives of Maintenance Therapy

Prevent opiate or other drug withdrawal (if a characteristic of a specific drug)

Prevent drug craving or drug hunger

Normalize physiologic function

Maintain at tolerance threshold to prevent euphoria

Prevent continued or recurrent use of illicit opiates or other targeted drugs of abuse

Allow psychologic and sociologic issues leading to drug use to be addressed by appropriate behavioral and other techniques

MAINTAIN ABSTINENCE, THAT IS, BE FREE OF ILLICIT USE OF DRUGS

teristics are essential (Table 4) (15). First, the medication must be effective after oral administration. Utilizing a parenteral agent carries with it the reinforcement of the conditioned responses related to intravenous self-administration that existed with heroin use. Second, the medication must have a long biological half-life so that an individual neither focuses on taking this substance more than once a day nor becomes excessively concerned when a dose is missed. Third, there must be minimal side effects associated with administration of the medication and no serious adverse effects. Fourth, the medication must be easy to use for a substantial percentage of persons addicted to heroin. Based on these objectives, therefore, the legalization of heroin or the establishment of heroin maintenance, irrespective of any moral issues, would be completely inappropriate (13, 15) (Table 5).

Methadone Maintenance

In reviewing these requirements, Dole et al. concluded in 1964 that the best and, at that time, only available synthetic opioid substance meeting such characteristics was methadone (Table 6) (14). Subsequently, a second agent, levo-alpha-acetylmethadol [LAAM], a congener of methadone which has an even longer half-life in humans (15, 16), was studied and approved, and utilized in treatment by the FDA. In fact, at that time, methadone was being used to treat chronic cancer pain. This is not surprising, since the same characteristics that made methadone attractive for maintenance therapy made it equally attractive for its use with chronic pain. Dole et al.

TABLE 4
Profile for a Potential Pharmacotherapeutic Agent for Treatment of Addiction

1. Effective after oral administration
   - Minimal systemic bioavailability after oral administration > 35%
   - Optimal systemic bioavailability after oral administration > 70%

2. Long biological half-life in humans
   - Plasma apparent terminal half-life > 20–24 hours
   - Specific receptor occupancy of > 20–24 hours

3. Minimal side effects during chronic administration

4. Safe, i.e., no true toxic or serious adverse effects

5. Efficacious for a substantial percentage of persons with the disorder (But does not need to be 90–100%; may be suitable for a small subset only — 15–20%)

TABLE 5
*Heroin Versus Methadone**

	Heroin	Methadone
Route of Administration	Intravenous	Oral
Onset of Action	Immediate	30 minutes
Duration of Action	3–6 hours**	24–36 hours
Euphoria	First 1–2 hours	None (if appropriate dose used)
Withdrawal Symptoms	After 3–4 hours	After 24 hours

* Effects of high dosages of drug or therapeutic agent in tolerant individuals.
** Includes action of major metabolite, morphine.

TABLE 6
Characteristics of Methadone in Maintenance Therapy

Highly Effective Orally
Bioavailability — 70–90%
Plasma levels in 30 minutes — peaks 2–4 hours
Steady state for 24 hours
Minimal withdrawal symptoms if dose is missed

Minimal Side Effects
Sweating   —   50%
Constipation   —   20%
No serious side effects at 25 years follow-up

Effectiveness
Successful in cessation of illicit opiate use — 60–90%

Dose dependent

Cost effective

demonstrated that methadone could be administered orally in a single daily dose, rather than 3–4 times a day. Subsequent studies showed that methadone has a duration of action in humans of 24–36 hours as contrasted with the 4-6 hours of heroin and morphine (14, 15). Furthermore, it was demonstrated that those patients who were placed on methadone with an initial dose of 20–40 mg/day and a stepwise dose increase of 5–10 mg every 4–7 days until a dose of 80–120 mg was reached, developed a tolerance threshold which other opioids could not overcome (14). The higher the dose of methadone, the greater the "blocking" effect of euphoria from heroin and other short-acting opioids. Furthermore, these investigators found that when a patient was being maintained on methadone, intravenous injection of comparable doses of methadone or of any other opioid tested were not associated with any narcotic effect, including respiratory depression or euphoria.

The subsequent initiation of methadone maintenance for heroin dependency and its effectiveness in diminishing heroin use are well known by others (18). However, it is important to emphasize that studies have demonstrated that, with respect to the effects on the neuroendocrine system and immune function, maintenance therapy with methadone has been shown to reverse the abnormalities seen with heroin addiction, and does it without any toxic or serious side effects (15, 16). In reviewing the pharmacological actions of methadone, it is not surprising to find that this effectiveness has been demonstrated. When considering its pharmacokinetics, it would be surprising were this not the case. It is also important to emphasize that maintenance therapy with methadone will be effective only for opioid drugs, and will not have any effect in preventing withdrawal from or craving for any other group of mood-altering substances. It may also be belaboring the obvious to reiterate that methadone will be most effective in programs that combine maintenance with counseling, psychological support, education, and retraining.

Despite these observations and the elucidation of the principles of methadone maintenance during the previous three decades, the majority of health care providers have little or no understanding of either the concept of maintenance or the neurobiological actions of methadone. This lack of understanding is also prevalent in individuals running maintenance programs which have enrolled approximately 179,000 persons (19, 20). This lack of understanding also explains why the majority of patients on maintenance therapy are being treated with doses insufficient to raise their tolerance threshold high enough to prevent intravenous use of heroin. To reverse this situation, the neurobiology of opioid dependence and pharmacokinetics of these drugs must be appreciated if better approaches to the treatment of heroin addiction are to be achieved.

All clinical investigations described in this manuscript were conducted in accord with the guidelines of the Declaration of Helsinki and have been approved by the Institutional Review Board at The Rockefeller University Hospital.

Also, all experiments on animals reported in this manuscript were conducted in accord with the National Institutes of Health (US) guidelines for the care and use of laboratory animals and have been approved by the institutional office at The Rockefeller University which supervises such work.

Acknowledgments

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