library/ASC95/ASC95.html.
43. Unpublished estimate from analysis of the 1993 National Household Survey on Drug Abuse, provided by S. Everingham and E. Chen of the RAND Corporation.
44. Specifically, $P(\text{cocaine} \mid \sim\text{marijuana}) = [P(\text{cocaine}) - P(\text{cocaine} \mid \text{marijuana}) \times P(\text{marijuana})]/P(\sim\text{marijuana}) = (0.06 - 0.22 \times 0.28)/0.72 = 0.00$ within rounding error.
45. A. Goldstein, *Addiction: From Biology to Drug Policy* (Freeman, New York, 1994).
46. R. MacCoun and P. Reuter, *Beyond the Drug War: Learning from Other Places, Times, and Vices* (Cambridge Univ. Press, New York, forthcoming).
47. T. Cook and D. Campbell, *Quasi-Experimentation: Design and Analysis Issues for Field Settings* (Houghton Mifflin, Boston, 1979).
48. R. J. MacCoun, K. Model, H. Phillips-Shockley, P. Reuter, in *Policies and Strategies to Combat Drugs in Europe*, G. Estievenart, Ed. (Martinus Nijhoff, Dordrecht, Netherlands, 1995).
49. J. A. Miron and J. Zweibel, *Am. Econ. Rev.* **81**, 242 (1991).
50. R. MacCoun, P. Reuter, T. Schelling, *J. Policy Anal. Manag.* **15**, 330 (1996); M. A. R. Kleiman, *Against Excess: Drug Policy for Results* (Basic Books, New York, 1992).
51. R. Hartnoll, *Multi-City Study: Drug Misuse Trends in Thirteen European Cities* (Council of Europe, Strasbourg, France, 1994).
52. European Monitoring Centre for Drugs and Drug Addiction, *1995 Annual Report on the State of the Drugs Problem in the European Union* (European Communities, Lisbon, Portugal, 1996).
53. The research reported here was supported by a grant from the Alfred P. Sloan Foundation to RAND's Drug Policy Research Center. Our arguments are developed in greater detail (*46*). We thank J. Caulkins, P. Cohen, P.Cook, M. Farrell, M. Feinleib, M. Kleiman, and F. Zimring for helpful comments, and B. Kilmer for research assistance.

Drug Abuse: Hedonic Homeostatic Dysregulation

George F. Koob* and Michel Le Moal

Understanding the neurobiological mechanisms of addiction requires an integration of basic neuroscience with social psychology, experimental psychology, and psychiatry. Addiction is presented as a cycle of spiralling dysregulation of brain reward systems that progressively increases, resulting in compulsive drug use and a loss of control over drug-taking. Sensitization and counteradaptation are hypothesized to contribute to this hedonic homeostatic dysregulation, and the neurobiological mechanisms involved, such as the mesolimbic dopamine system, opioid peptidergic systems, and brain and hormonal stress systems, are beginning to be characterized. This framework provides a realistic approach to identifying the neurobiological factors that produce vulnerability to addiction and to relapse in individuals with a history of addiction.

Most definitions of drug addiction or substance dependence include (i) descriptions of "overwhelming involvement with the use of a drug (compulsive use)" (*1*) and (ii) a number of symptoms or criteria that reflect a loss of control over drug intake and a narrowing of the number of different behavioral responses toward drug-seeking (*2*). Drug addiction can be equated with substance dependence as defined by the American Psychiatric Association (*3*). However, it is important to distinguish between what is termed substance use, substance abuse, and substance dependence (addiction) (*4*).

In humans, most drug users do not become drug abusers or drug-dependent (*4*). Similarly, stable drug intake can be observed in animals without pronounced signs of dependence, even with intravenous drug administration under limited-access situations. Many factors such as availability (route of administration), genetics, history of drug use, stress, and life events contribute to the transition from drug use to drug addiction. The current challenge is to discover what neurobiological elements convey the individual differences in vulnerability to this transition to drug addiction.

In this article we will draw from recent formulations in behavioral neuroscience and other disciplines to construct a framework to view addiction as a continuous process of hedonic homeostatic dysregulation. Multiple sources of reinforcement are identified in the spiralling cycle of addiction, and the symptoms of this hedonic dysregulation form the well-known criteria for substance dependence or addiction (*2*, *3*). Critical neurotransmitters, hormones, and neurobiological sites have been identified that may mediate the hedonic dysregulation and may provide the substrates that convey both vulnerability to, and protection against, drug addiction (*5*) (Fig. 1).

Spiralling Distress and the Addiction Cycle

Important elements that may be involved in the failure to self-regulate drug use, as well as other behaviors such as compulsive gambling and binge eating, have derived from social psychology (*6*). It is of interest to conceptualize how these regulation failures ultimately lead to addiction in the case of drug use or an addiction-like pattern with nondrug behaviors. Lapse-activated causal patterns, that is, patterns of behavior that contribute to the transition from an initial lapse in self-regulation to a large-scale breakdown in self-regulation, can lead to spiralling distress (*6*). Spiralling distress describes how, in some cases, the first self-regulation failure can lead to emotional distress, which sets up a cycle of repeated failures to self-regulate, and where each violation brings additional negative affect (*6*). For example, a failure of strength may lead to initial drug use or relapse, and other self-regulation failures can be recruited to prevent an exit from the addiction cycle. Here, spiralling distress will be used to describe the progressive dysregulation of the brain reward system within the context of repeated addiction cycles (Fig. 1A).

Psychiatry and experimental psychology, in effect, address the same addiction cycle (Fig. 1B), and neurobiology has begun to identify the neurobiological elements that contribute to the break with hedonic homeostasis, known as addiction. Although animal models provide a critical part of the study of the neurobiology of addiction, no animal models incorporate all the elements of addiction. Alternatively, animal models can be established and validated for different symptoms or constructs associated with addiction (*7*). There is much evidence for valid animal models of many of the criteria in the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (*3*) and the sources of reinforcement associated with addiction (*7*).

Neurobiology of Drug Reinforcement

The focus for the neurobiological mechanism for the positive-reinforcing effects of drugs of abuse has been the mesocorticolimbic dopamine system and its connections in the basal forebrain (*8*, *9*). For cocaine, amphetamine, and nicotine, the facilitation of dopamine neurotransmission in the mesocorticolimbic dopamine system appears to be critical for the acute reinforcing actions of these drugs [for re-

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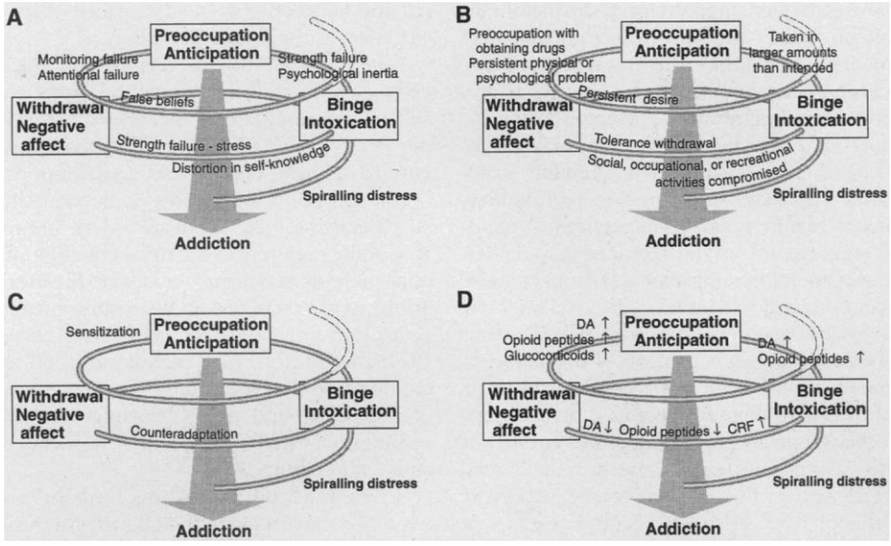

Fig. 1. Diagram describing the spiralling distress–addiction cycle from four conceptual perspectives: social psychological, psychiatric, dysadaptational, and neurobiological. (**A**) The three major components of the addiction cycle, preoccupation-anticipation, binge-intoxication, and withdrawal–negative affect, and some of the sources of potential self-regulation failure in the form of underregulation and misregulation. (**B**) The same three major components of the addiction cycle with the different criteria for substance dependence from DSM-IV incorporated. (**C**) The places of emphasis for the theoretical constructs of sensitization and counteradaptation. (**D**) The hypothetical role of different neurochemical and endocrine systems in the addiction cycle. Small arrows refer to increased functional activity. DA, dopamine, CRF, corticotropin-releasing factor. Note that the addiction cycle is conceptualized as a spiral that increases in amplitude with repeated experience, ultimately resulting in the pathological state known as addiction.

views, see (*8*, *9*)]. Multiple dopamine receptors including D-1, D-2, and D-3 have been implicated in this reinforcing action (*10*, *11*). Neuropharmacological studies support both a dopamine-dependent and a dopamine-independent contribution to the positive-reinforcing effects of opiates such as heroin (*8*, *9*, *12*). Ethanol appears to interact with ethanol-sensitive elements in multiple neurotransmitter receptor systems, and these interactions may contribute to ethanol's positive-reinforcing actions (*13*). The neurotransmitters and receptor systems implicated include actions on the γ-aminobutyric acid (GABA), glutamate, dopamine, serotonin, and opioid peptide systems, all of which are within the mesocorticolimbic dopamine system and its connections to the nucleus accumbens and amygdala (*13*). Limited study has implicated the release of dopamine in the nucleus accumbens in the positive-reinforcing actions of tetrahydrocannabinol (THC) (*14*).

A major question still challenging drug abuse research, however, is whether the neurobiology of reward and drug reinforcement changes with chronic use and during the manifestation of an abstinence syndrome when the drug is no longer self-administered. Historically, substance dependence has focused on the manifestation of an abstinence syndrome upon abrupt cessation of drug administration that was characterized by physical signs such as the well-documented tremor and autonomic hyperactivity of ethanol withdrawal and the discomfort and pain associated with opiate withdrawal. However, recent conceptualizations of abstinence symptoms have begun to focus on aspects of abstinence that are common to all drugs of abuse and may be considered more motivational in nature and perhaps are best described as a negative affective state (*5*, *15*, *16*). These symptoms include various negative emotions such as dysphoria, depression, irritability, and anxiety (*3*, *15*, *16*).

Consistent with these clinical observations, animal studies in which intracranial self-stimulation was used as a measure of reward function have revealed pronounced decreases in reward (or increases in the reward threshold) associated with withdrawal from all major drugs of abuse tested to date (Fig. 2). These effects vary with dose and duration of exposure to the drug, but can last as long as 96 hours after withdrawal from the drug in rodent models (*15*, *16*).

The significance of drug abstinence syndromes remains controversial as a basis for compulsive use (*1*, *7*), but increasing evidence both in animal and human studies suggests that the presence of a negative affective state may not only signal the beginning of the development of dependence (*17*), but may contribute to vulnerability to relapse and may also have motivational significance. Rats made dependent on opiates and ethanol show increases in drug self-administration (*18*). Thus, exposure to sufficient amounts of drug to produce dependence as measured by elevations in reward thresholds can increase the motivation for a drug. This increase could result from additive or even synergistic sources of positive and negative reinforcement (*19*) and may contribute to the addiction cycle.

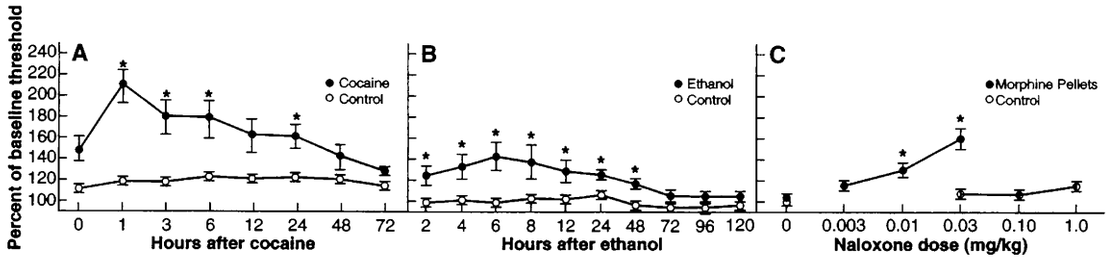

Fig. 2. Changes in reward threshold associated with chronic administration of three major drugs of abuse. Reward thresholds were determined by a rate-independent discrete trials threshold procedure for intracranial self-stimulation (ICSS) of the medial forebrain bundle. (**A**) Rats equipped with intravenous catheters were allowed to self-administer cocaine for 12 hours before withdrawal and reward threshold determinations. Elevations in threshold were dose-dependent with longer bouts of cocaine self-administration yielding larger and longer-lasting elevations in reward thresholds (*51*). Asterisks refer to significant differences between treatment and control values. Values are mean ± SEM. (**B**) Elevations in reward thresholds with the same ICSS technique after chronic exposure to ethanol of about 200 mg% in ethanol vapor chambers (*52*). (**C**) Elevations in reward thresholds measured with the same ICSS technique after administration of very low doses (in milligrams per kilogram of body weight) of the opiate antagonist naloxone to animals made dependent on morphine with two, 75-mg morphine (base) pellets implanted subcutaneously (*53*).

Neural Substrates for Sensitization and Counteradaptation of Reward

At the neurobiologial level, two neuroadaptive models have been conceptualized to explain the changes in motivation for drug-seeking that reflect compulsive use: counteradaptation and sensitization. Counteradaptation hypotheses (*20*) were intimately linked to the development of hedonic tolerance by the formulation known as opponent process theory (*21*). In contrast, sensitization, a progressive increase in a drug's effect with repeated administration, has been conceptualized to be a shift in an incentive-salience state (*21*).

Both of these conceptual positions focus on neurobiological changes at the molecular, cellular, and system levels, and both may involve what have been described as "within-system" and "between-system" changes (*8*). At the neurochemical level, changes associated with the same neurotransmitters implicated in the acute reinforcing effects of drugs that are altered during the development of substance dependence would be examples of within-system changes.

Counteradaptive, within-system neurochemical events include decreases in dopaminergic and serotonergic neurotransmission in the nucleus accumbens during drug withdrawal (*22*). At the molecular and cellular levels, changes in opiate receptor function during withdrawal from chronic opiates and decreased GABAergic and increased glutamatergic transmission during ethanol withdrawal have been observed [(*23*), and Nestler and Aghajanian (*24*) in this issue)]. Sensitization to the locomotor stimulant effects of psychomotor stimulants and opiates also appears to involve within-system activation of the mesolimbic dopamine system. There appears to be a time-dependent chain of adaptations within the mesolimbic dopamine system that leads to the long-lasting changes produced by sensitization (*25*).

Changes in other neurotransmitter systems that are not linked to the acute reinforcing effects of the drug but are recruited during chronic drug administration have been conceptualized as between-system adaptations. Examples of between-system counteradaptations include increases in dynorphin function in the nucleus accumbens during chronic cocaine administration, increases in anti-opioid peptides associated with chronic opioid administration, and augmentation of brain stress systems such as corticotropin-releasing factor (CRF) associated with cocaine, opiates, ethanol, and THC (*15, 16, 26*).

Recent neuroanatomical, neurochemical, and neuropharmacological observations have provided support for a distinct brain circuit within the basal forebrain that may mediate both the within-system and between-system neurochemical changes associated with drug reward. The extended amygdala (*27*) is a hypothesized macrostructure consisting of several basal forebrain structures that share similarities in morphology, neurochemistry, and connectivity (*27*). Support for the role of the extended amygdala in the acute reinforcing effects of drugs of abuse can be found in a series of in vivo microdialysis and neuropharmacological studies that showed selective activation of dopamine in the shell of the nucleus accumbens by most of the major drugs of abuse (*28*). In addition, GABAergic and opioidergic mechanisms in the central nucleus of the amygdala may participate in the acute reinforcing actions of ethanol (*29*). Also, the central nucleus of the amygdala may function in counteradaptation of the brain reward system during the development of drug dependence. Chronic administration of drugs can alter both CRF and proopiomelanocortin gene expression in the amygdala (*30*). An increased CRF response in the central nucleus of the amygdala is associated with acute withdrawal from ethanol, opiates, cocaine, and THC (*31*).

Limited data suggest a specific role for parts of the extended amygdala in sensitization. The mesolimbic dopamine system is clearly involved, but no specific subregion has been delineated. Glucocorticoids can activate the mesolimbic dopamine system by increasing dopamine synthesis, decreasing dopamine metabolism, and decreasing catecholamine uptake (*5*). The participation of a specific subprojection of the mesolimbic system in sensitization is under investigation.

Relapse: Neural Substrates and Vulnerability

Relapse and vulnerability to relapse are key elements in the maintenance of a chronic relapsing disorder such as addiction [see O'Brien (*32*), this issue]. Animal models predictive of relapse are being developed. Studies suggest that stresslike stimuli and neuropharmacological agents that activate the mesocorticolimbic dopamine system can rapidly reinstate intravenous drug self-administration that has been previously extinguished (*33*), and drugs that modulate dopamine receptors can block reinstatement of cocaine self-administration in rats (*11*). Naltrexone and acamprosate decrease relapse rates in alcoholics (*34*) and can modify excessive drinking in rodents in various models (*35*). Thus, a rich source for study of the neurobiological mechanisms of relapse will be the same neurotransmitters and neurocircuitry implicated in the within- and between-system adaptations of sensitization and counteradaptation.

The vulnerability to relapse will have both genetic and environmental bases resulting in a susceptible host, from a medical perspective (*36*). Animal studies have begun to address both these contributions. While genetic vulnerability is beyond the scope of this review, there are rodent strains that show preferences for drinking ethanol, and there is mounting evidence of alterations in the same reward neurotransmitters that may form the basis of such preferences (*37*). In addition, new techniques such as quantitative trait loci analysis and the study of knock-out and transgenic mice are revealing potential genetic sites associated with vulnerability (*38*).

Environmental factors involved in vulnerability have largely focused on the role of stress. An atypical responsivity to stress in former opiate- and cocaine-dependent subjects has been well documented and hypothesized to be linked to chronic relapse (*39*). Exposure to repeated stressors also increases the propensity to develop initial intravenous drug self-administration (acquisition) (*40*) and can facilitate reinstatement of drug self-administration after extinction (relapse) (*33*). These effects appear to be directly linked to activation of the hypothalamic pituitary adrenal axis. Suppression of stress-induced corticosterone secretion abolishes the enhanced behavioral responsiveness to amphetamine and morphine produced by different stressors (*41*). Consistent with these observations, repeated administration of corticosterone can substitute for stress and increase the behavioral effects of psychostimulants (*41*). It is hypothesized that glucocorticoid hormones function in the long-term maintenance of the sensitized state and may even represent a within-system change (*41*). In addition, vulnerability to drug-taking may be influenced by a history of drug experience and the presence of competing nondrug reinforcers altering the response to drug reinforcers (*42*).

The combination of genetic and environmental factors can dramatically change an animal's response to drugs. A comparison of rats that show a high and low locomotor response to forced exposure in a novel environment revealed that high responders (HRs) show a greater propensity to develop intravenous drug self-administration compared with low responders (LRs) (*43*). This greater sensitivity to drugs in HRs shows a correlation with dysregulation of the hypothalamic pituitary adrenal axis (a prolonged secretion of corticosterone in response to stress) and with a higher sensitivity to the behavioral and dopamine-activating effects of glucocorticoids (*41*) (Fig. 3).

Indeed, stress has been hypothesized to cause HR rats to express enhanced responses to drugs (*43*, *44*). What is largely unknown is how these genetic and environmental factors combine to contribute to the development of what constitutes substance dependence (addiction) in humans. In addition, identification of the vulnerability for different parts of the addiction cycle using animal models will provide clues to relapse vulnerability in human addicts. With the use of animal models, studies of the interaction of genetics, of stress, and of the initial response to drugs on various features of the addiction cycle other than drug-taking will be informative.

Homeostasis of Reward, Self-Regulation, and "Natural" Addictions

The concept of homeostasis contends that an organism maintains equilibrium in all of its systems, including the brain reward system, that is, the organism uses physiological and cognitive or behavioral capabilities to function within the appropriate limits of physiology with the help of its own resources. Environmental factors that challenge homeostasis are met with counter actions. Allostasis refers to the concept of physiology where an organism must vary all of the parameters of its internal milieu and match them appropriately to perceived and anticipated environmental demands in order to maintain stability (*45*). If the threats to the system continue to produce disequilibrium, the process of allostasis continues to regulate where the organism must mobilize enormous amounts of energy to maintain apparent stability at a now pathological "set point." The system is at the limit of its capability, and thus a small challenge can lead to breakdown (*45*). This is the beginning of spiralling distress and the addiction cycle. When the organism has reached a state of dysregulation so severe that it cannot recover by mobilizing its own resources, allostasis has reached the point of what is normally considered illness. The state of dysregulation of the reward system may produce loss of control over drug intake, compulsive use, or drug addiction. The mechanisms that contribute to this allostasis are normal mechanisms for homeostatic regulation of reward that have spun out of the physiological range (that is, sensitization and counteradaptation).

Addiction Cycle: Sensitization and Counteradaptation

The role of sensitization in dependence has been elaborated where a shift in an incentive-salience state, described as "wanting," progressively increases with repeated exposure to drugs of abuse (*21*). This shift is largely attributed to a pathological overactivity of mesolimbic dopamine function and, as such, represents a break with homeostasis. Other factors such as increased secretion of glucocorticoids may function in the long-term maintenance of this sensitized state (*41*).

Early theories of counteradaptation with chronic drug administration were based on the concept of homeostasis (*20*) and later extended to hedonic processes in opponent process theory (*21*) (Fig. 4). This theory may explain the affective withdrawal component of the addiction cycle and also may explain how repeated drug-taking can lead to spiralling distress. Indeed, the onset of a negative affective state can be used to define addiction (*17*). In addition, the negative affective state may have motivating properties in maintaining drug-seeking behavior, not only by direct negative reinforcement (that is, the drug is taken to relieve the negative state) but also by changing the set point for the efficacy of reinforcers and thus add motivational effectiveness to both positive drug effects and conditioned positive drug effects (*7*, *15*, *16*, *21*). At least two common neurochemical elements, activation of limbic CRF systems and a decrease in mesolimbic DA function, are common neurochemical correlates of the early parts of drug withdrawal (*15*, *16*, *31*).

At first glance, the two processes of sensitization and counteradaptation may appear to make opposite predictions about the course of drug dependence and the neurobiology of drug dependence. However, if drug dependence is viewed in the context of spiralling distress, then it is possible that both processes are active, although perhaps not concurrently, at different parts of the cycle (Figs. 1 and 4). The neurobiology of a heavily dependent person (Fig. 4C) will be very different from that of a nondependent person (Fig. 4A) and may reflect a state of severe allostasis (with a change in set point) and the part of the addiction cycle associated with negative affect and spiralling distress (Fig. 1C). For example, enhanced dopaminergic and opioidergic neurotransmission may be involved in the preoccupation-anticipation stage and result in sensitization (Figs. 1C and 4B), but compromised dopamine, serotonin, and opioidergic neurotransmission, as well as increases in stress neurotransmitters, may be responsible for the negative affective state of withdrawal (Figs. 1D and 4C). The combination of a change in hedonic set point produced by repeated counteradaptation and a separate mechanism for sensitization would provide a dramatic motivational force for continuing drug dependence (Fig. 4, C and D).

This view is similar to that of incentive motivational theory (*46*) and incorporates some aspects of incentive-salience theory (*21*). Under the current formulation, counteradaptation creates a need state that may or may not easily be labeled by subjective responses but, rather, reflects a chronic break with homeostasis such as a decrease in hedonic set point. Sensitization, in contrast, creates a facilitated incentive motivation or incentive salience that reflects enhanced responses to drug incentive stimuli (that is, wanting or craving).

According to this formulation, sensitization is assigned a relatively minor role in the ongoing process of spiralling distress, but a more important role in triggering the beginning of instability (vulnerability to drug-taking, as in the form of cross-sensitization to stress) or retriggering of instability as in the process of relapse (reentrance into the cycle of spiralling distress). Indeed, a dependent person is almost by definition already sensitized. However, there is little

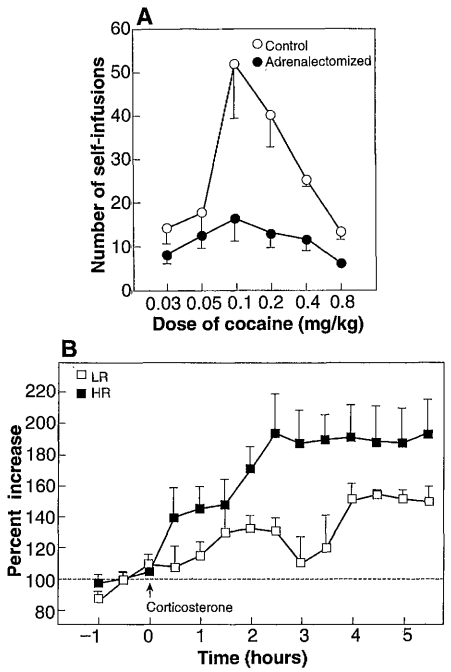

Fig. 3. (**A**) The effects of adrenalectomy on cocaine self-administration in rats. Animals were trained to self-administer cocaine by nose-poking and subjected to a dose-effect function. Adrenalectomy produced a flattening of the dose-effect function, with decreases of cocaine intake at all the doses (*54*). (**B**) Corticosterone-induced changes in extracellular concentrations of dopamine in high-responding (HR) and low-responding (LR) animals. HR animals that drank the corticosterone solution (100 mg/ml) in the dark period showed a faster and higher increase in accumbens dopamine than LR animals (*55*).

evidence of sensitization in drug-dependent people, and most clinical evidence points to tolerance, not sensitization. Human addicts consume enormous amounts of ethanol, opiates, and even stimulants that would easily be toxic to nonaddicted individuals (*47*). In addition, most of the animal studies of sensitization have focused either on locomotor activity as a dependent variable or in the drug reward domain on acquisition of drug self-administration (*21*). If sensitization is to gain a role as extensive as that outlined herein, more data will be required to show a link between these measures of enhanced sensitivity to drugs of abuse (locomotor activity and acquisition of drug self-administration) and other measures of dependence.

Implications for the Concept of Addiction and Treatment

The present conceptualization of addiction has important implications for the treatment of drug addiction. The social psychological components of failure to self-regulate may impact on different parts of the addiction cycle (Fig. 1A), and these different components may be reflected in changes in different components of reward neurocircuitry (Fig. 1D). For example, failure of strength may reflect increases in stress system activity, whereas failure of monitoring or attention may reflect cognitive changes that are influenced by the widely distributed brain monoamine systems.

The present conceptualization also provides a framework for studying the components of addiction most often neglected in animal studies. The role of neurobiology in different processes, such as social psychological self-regulation failures, positive and negative reinforcement, sensitization, and counteradaptation, changes dramatically over the course of transition from drug use to abuse to addiction. In addition, different drugs may act differentially on parts of the spiralling distress–addiction cycle. Young, type II alcoholics (*48*) may be more involved in the preoccupation-anticipation and binge components than terminal alcoholics, where a major need state has usurped most other sources of motivation. In contrast, users of opiates and nicotine may assume this need-state component at a much earlier stage (*49*). Studies of the neurobiology of such differences will be critical for future interventions at both the prevention and treatment levels.

There is clearly a neurobiological basis for multiple sites of treatment intervention. Eliminating affective withdrawal and the reward need state are critical (such as methadone for opiate addiction), as well as eliminating the changes that lead to facilitated incentive salience (such as naltrexone for alcohol addiction). Various forms of behavioral therapies and psychotherapy have been shown to be effective in treating addiction, particularly in combination with pharmacotherapy [(*34*) and O'Brien (*32*), this issue]. These therapies ultimately act on the same dysregulated hedonic circuitry to help return and maintain it within homeostatic boundaries. In addition, vulnerability to addiction can be conveyed at any part of the spiralling distress of the addiction cycle and should not be simply relegated to initial drug responses.

Although beyond the scope of the present review, dysregulation of hedonic homeostasis can also occur with compulsive use of nondrug reinforcers. Similar patterns of spiralling distress–addiction cycles have been observed with pathological gambling, binge eating, compulsive exercise, compulsive sex, and others (*6*). The same neurobiological dysregulations and breaks with homeostasis may be occurring within the same neurocircuitry implicated in drug dependence. With the advent of more sophisticated measures of brain function in humans, such questions may be pursued.

The implications of this homeostatic view for everyday existence forces one to return to social psychology, but with a biological perspective. The brain hedonic system may be a limited resource (*50*). One can expend this resource rapidly in a binge of drug-taking or other compulsive behavior, but at a great risk for entrance into the spiralling dysregulation of the addiction cycle. Alternately, one can adopt a more regulated, "hedonic Calvinistic" approach (*51*) where use of the reward system is restricted within the homeostatic boundary (that is, without the development of subsequent negative affect). Such an ascetic view may or may not fall within certain cultural norms, but probably makes biological sense.

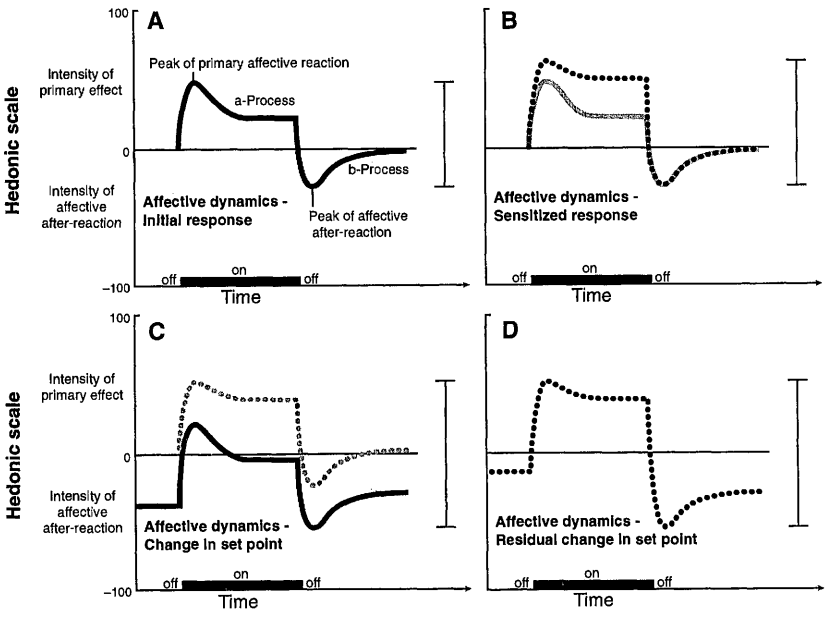

Fig. 4. Diagram illustrating an extension of Solomon and Corbit's opponent-process model of motivation to incorporate the conceptual framework of this article (*21*). All panels represent the affective response to the presentation of the stimuli (that is, drug administration). (**A**) The original description of the affective stimulus, which was argued to be a sum of both an a-process and a b-process and represents the initial experience with no prior drug history. (**B**) The same affective stimulus in an individual with an intermittent history of drug use that may result in sensitized response. The shaded line illustrates the sametrace of the initial experience in (A). The dotted line represents the sensitized response. (**C**) Change in the affective stimulus hypothesized to exist in the heavily dependent individual (that is, after chronic exposure) where there is a major change in the hedonic set point. This represents a change sufficient to be considered a major break with hedonic homeostasis. The light dotted line represents the sensitized response observed in (B). (**D**) The hypothesized state of protracted abstinence and enhanced vulnerability to relapse with a history of chronic continuous experience. The change in this panel reflects the change in the affective response in an organism with a history of depen-dence where there is both a change in set point that is long-lasting and a residual sensitization. The bar to the right of each diagram illustrates the total peak-to-peak contrast between the lowest point in negative affect to the highest point in positive mood produced by a drug at any point in the addiction cycle. An alternative hypothesis still under consideration is that even during an intermittent sensitization pattern of drug-taking, the affective after-reaction (b-process) also may get progressively larger and larger (*21*). "On" refers to the "time on" of the hedonic stimulus, in this case the drug action. "Off" refers to the "offset" of the drug action.

REFERENCES AND NOTES

1. J. H. Jaffe, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, A. G. Gilman, T. W. Rall, A. S. Nies, P. Taylor, Eds. (Pergamon, New York, ed. 8, 1990), pp. 522–573.
2. World Health Organization, *International Statistical Classification of Diseases and Related Health Problems* (World Health Organization, Geneva, 10th revision, 1990).
3. *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, Washington, DC, ed. 4, 1994).
4. A recent Institute of Medicine report [Institute of Medicine, *Pathways of Addiction* (National Academy Press, Washington, DC, 1996)] used a three-stage conceptualization of drug-taking behavior that applies to all psychoactive drugs, whether licit or illicit: use, abuse, and dependence. "Use" of drugs is the taking of drugs, in the narrow sense, to distinguish it from a more intensified pattern of use. "Abuse" refers to any harmful use, regardless of whether the behavior constitutes a disorder in the DSM-IV of the American Psychiatric Association. "Dependence" refers to "substance dependence" as defined by DSM-IV or "addiction" as defined by International Classification of Diseases (ICD 10).
5. G. F. Koob and E. J. Nestler, *J. Neuropsychiatry Clin. Neurosci.* **9**, 482 (1997); P. V. Piazza and M. Le Moal, *Brain Res. Rev.*, in press.
6. Underregulation can be defined as a "failure to exert control over one's self." Conflicting or inadequate standards would be a breakdown in the basis for self-regulation. Reduction in monitoring is a failure of a person to evaluate one's self and actions against relevant standards. Inadequate strength is analogous to the common-sense concept of willpower and is a conflict between the power of impulse/tendency to act and the self-regulatory mechanism to interrupt that response and prevent action. Misregulation can be defined as "exerting control in a way that fails to bring about the desired result or leads to some alternative result." Misregulation probably most often involves some kind of deficiency in knowledge, especially self-knowledge. These knowledge deficiencies include false beliefs, distorted beliefs, overgeneralizations, and misdirected control efforts. Lapse-activated causal patterns are the patterns of behavior that translate an initial lapse (break in self-regulation) into a large-scale indulgence or major binge. Many factors contribute to these patterns of behavior, including underregulation, emotional responses, stress, zero-tolerance beliefs, spiralling distress, and others [R. F. Baumeister, T. F. Heatherton, D. M. Tice, Eds., *Losing Control: How and Why People Fail at Self-Regulation* (Academic Press, San Diego, 1994)].
7. The use of animal models to characterize the neurobiology of specific aspects of human disorders is a reorientation to the "top-down" approach. Here, specific behaviors are explored at the system level, the cellular level, and ultimately the molecular level, with hypothesis testing based on an understanding of the mechanism of the behavioral response [A. Markou *et al.*, *Psychopharmacology* **112**, 163 (1993); G. F. Koob, in *Psychopharmacology: The Fourth Generation of Progress*, F. E. Bloom and D. J. Kupfer, Eds. (Raven Press, New York, 1995), pp. 759–772; G. F. Koob *et al.*, *J. Psychopharmacol.*, in press].
8. G. F. Koob and F. E. Bloom, *Science* **242**, 715 (1988).
9. R. A. Wise and P.-P. Rompre, *Annu. Rev. Physiol.* **40**, 191 (1989); M. Le Moal and H. Simon, *Physiol. Rev.* **71**, 155 (1991); G. F. Koob, *Trends Pharmacol. Sci.* **13**, 177 (1992); F. E. Pontieri, G. Tanda, F. Orzi, G. Di Chiara, *Nature* **382**, 255 (1996).
10. W. L. Woolverton, *Pharmacol. Biochem. Behav.* **24**, 531 (1986); G. F. Koob, H. T. Le, I. Creese, *Neurosci. Lett.* **79**, 315 (1987); J. Bergman, J. B. Kamien, R. D. Spealman, *Behav. Pharmacol.* **1**, 355 (1990); S. B. Caine and G. F. Koob, *Science* **260**, 1814 (1993).
11. D. W. Self, W. J. Barnhart, D. A. Lehman, E. J. Nestler, *Science* **271**, 1586 (1996).
12. G. Di Chiara and R. A. North, *Trends Pharmacol. Sci.* **13**, 185 (1992); T. S. Shippenberg, A. Herz, R. Spanagel, R. Bals-Kubik, C. Stein, *Ann. N. Y. Acad. Sci.* **654**, 347 (1992).
13. G. F. Koob, F. J. Vaccarino, M. Amalric, F. E. Bloom, in *Brain Reward Systems and Abuse*, J. Engel and L. Oreland, Eds. (Raven Press, New York, 1987), pp. 35–50; J. A. Engel *et al.*, in *Novel Pharmacological Interventions for Alcoholism*, C. A. Naranjo and E. M. Sellers, Eds. (Springer, New York, 1992), pp. 68–82; E. M. Sellers, G. A. Higgins, M. B. Sobell, *Trends Pharmacol. Sci.* **13**, 69 (1992); B. Tabakoff and P. L. Hoffman, in *Substance Abuse: A Comprehensive Textbook*, J. H. Lowinson, P. Ruiz, R. B. Millman, Eds. (Williams & Wilkins, Baltimore, 1992), pp. 152–185.
14. J. P. Chen, W. Paredes, J. H. Lowinson, E. L. Gardner, *Neurosci. Lett.* **129**, 136 (1991); G. Tanda, F. E. Pontieri, G. Di Chiara, *Science* **276**, 2048 (1997).
15. A. Markou and G. F. Koob, *Neuropsychopharmacology* **4**, 17 (1991).
16. G. F. Koob, A. Markou, F. Weiss, G. Schulteis, *Semin. Neurosci.* **5**, 351 (1993); G. F. Koob, *Neuron* **16**, 893 (1996).
17. Russell argued, "The notion of dependence on a drug, object, role, activity, or any other stimulus-source requires the crucial feature of negative affect experienced in its absence. The degree of dependence can be equated with the amount of this negative affect, which may range from mild discomfort to extreme distress, or it may be equated with the amount of difficulty or effort required to do without the drug, object, etc." This appearance of negative affect could have motivational significance or simply be a signal of a change in set point [M. A. H. Russell, in *Drugs and Drug Dependence*, G. Edwards, M. A. H. Russell, D. Hawks, M. MacCafferty, Eds. (Saxon House/Lexington Books, Westmead, UK, 1976), pp. 182–187].
18. M. R. A. Carrera, G. Schulteis, G. F. Koob, *Neurosci. Abstr.* **21**, 725 (1995); A. J. Roberts, M. Cole, G. F. Koob, *Alcohol. Clin. Exp. Res.* **20**, 1289 (1996).
19. A. Ettenberg, S. Sgro, N. White, *Physiol. Behav.* **28**, 873 (1982).
20. C. K. Himmelsbach, *Federation Proc.* **2**, 201 (1943).
21. In reference to opponent process theory, the a-processes (positive hedonic effects) were proposed to occur shortly after presentation of the reinforcer and to show tolerance. In contrast, the b-processes (negative hedonic effects) appear after the a-process has terminated, are slow to decay, and get larger with repeated exposure. More recent data and conceptualizations suggest that the b-process actually may appear shortly after the beginning of the a-process and may ultimately result in a change in hedonic set point (Fig. 4). In reference to sensitization theory, sensitization has been defined as the increased response to a drug that follows its repeated intermittent presentation and may be a potential source of significant differential vulnerability to certain concepts of the addiction cycle. Sensitization theory invokes a shift to a state of incentive salience (defined as a hypersensitive neural state that produces the experience of "wanting"). This state of incentive salience is hypothesized to be produced by drug-induced sensitization of the mesocorticolimbic dopamine system. Thus, the pathologically strong craving or "wanting" encountered during protracted abstinence would be hypothesized to be due, in large part, to an overactive mesocorticolimbic dopamine system. Sensitization has largely been characterized as an enhanced motor response to drugs of abuse with repeated administration, though recent work has extended these effects to a progressive increase in the reinforcing value of the drugs, at least during initial acquisition of drug-seeking or conditioned drug effects (Figs. 1 and 4). Sensitization is also more likely to be evident with intermittent, rather than continuous, administration of drugs, which favors the development of tolerance, and sensitization is long-lasting (up to weeks after injection) [R. L. Solomon and J. D. Corbit, *Psychol. Rev.* **81**, 119 (1974); R. L. Solomon, in *Psychopathology: Experimental Models*, J. D. Maser and M. E. P. Seligman, Eds. (Freeman, San Francisco, 1977), pp. 124–145; T. E. Robinson and K. C. Berridge, *Brain Res. Rev.* **18**, 247 (1993); G. Schulteis and G. F. Koob, *Neurochem. Res.* **21**, 1437 (1996); J.-P. Laulin, A. Larcher, E. Celerier, M. Le Moal, G. Simonnet, *Eur. J. Pharmacol.*, in press].
22. F. Weiss, A. Markou, M. T. Lorang, G. F. Koob, *Brain Res.* **593**, 314 (1992); F. Weiss *et al.*, *J. Neurosci.* **16**, 3474 (1996).
23. E. J. Nestler, *J. Neurosci.* **12**, 2439 (1992).
24. _____ and G. K. Aghajanian, *Science* **278**, 58 (1997).
25. P. W. Kalivas and J. Stewart, *Brain Res. Rev.* **16**, 223 (1991); F. J. White and M. E. Wolf, in *The Biological Bases of Drug Tolerance and Dependence*, J. A. Pratt, Ed. (Academic Press, London, 1991), pp. 153–197; D. J. Henry and F. J. White, *Ann. N. Y. Acad. Sci.* **654**, 88 (1992).
26. D. H. Malin *et al.*, *Peptides* **11**, 277 (1990); T. S. Shippenberg, A. LeFevour, C. Heidbreder, *J. Pharmacol. Exp. Ther.* **276**, 545 (1996).
27. The extended amygdala includes the medial (shell) part of the nucleus accumbens, bed nucleus of the stria terminalis, the central medial amygdala, and the sublenticular substantia innominata region. The afferent and efferent connections of the extended amygdala make it well situated for mediating not only basic drug reward, but also the neuroadaptive changes associated with sensitization and counteradaptation. Afferent connections include projections from the limbic cortices, hippocampus, basolateral amygdala, midbrain, and lateral hypothalamus. Efferent connections include the ventral pallidum, ventral tegmental area, various brainstem projections, and a large projection to the lateral hypothalamus [J. B. Johnston, *J. Comp. Neurol.* **35**, 337 (1923); G. F. Alheid and L. Heimer, *Neuroscience* **27**, 1 (1988); L. Heimer and G. Alheid, in *The Basal Forebrain: Anatomy to Function*, T. C. Napier, P. W. Kalivas, I. Hanin, Eds. (Plenum, New York, 1991), pp. 1–42].
28. S. B. Caine, S. C. Heinrichs, V. L. Coffin, G. F. Koob, *Brain Res.* **692**, 47 (1995); M. P. Epping-Jordan, A. Markou, G. F. Koob, *Neurosci. Abstr.* **21**, 719 (1995); F. E. Pontieri, G. Tanda, G. Di Chiara, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 12304 (1995);
29. P. Hyytia and G. F. Koob, *Eur. J. Pharmacol.* **283**, 151 (1995); C. J. Heyser, A. J. Roberts, G. Schulteis, P. Hyytia, G. F. Koob, *Neurosci. Abstr.* **21**, 1698 (1995).
30. Y. Zhou *et al.*, *Eur. J. Pharmacol.* **315**, 31 (1996); Y. Zhou *et al.*, *J. Pharmacol. Exp. Ther.* **279**, 351 (1996).
31. S. Rassnick, S. C. Heinrichs, K. T. Britton, G. F. Koob, *Brain Res.* **605**, 25 (1993); S. C. Heinrichs, F. Menzaghi, G. Schulteis, G. F. Koob, L. Stinus, *Behav. Pharmacol.* **6**, 74 (1995); F. Rodríguez de Fonseca, M. R. A. Carrera, M. Navarro, G. F. Koob, F. Weiss, *Science* **276**, 2050 (1997); E. Merlo Pich *et al.*, *J. Neurosci.* **15**, 5439 (1995).
32. C. P. O'Brien, *Science* **278**, 66 (1997).
33. H. deWit and J. Stewart, *Psychopharmacology* **75**, 134 (1981); J. Stewart and H. deWit, in *Assessing the Reinforcing Properties of Abused Drugs*, M. A. Bozarth, Ed. (Springer-Verlag, New York, 1987), pp. 211–227; Y. Shaham, H. Rajabi, J. Stewart, *J. Neurosci.* **16**, 1957 (1996).
34. S. S. O'Malley *et al.*, *Arch. Gen. Psychiatry* **49**, 881 (1992); J. R. Volpicelli, A. I. Alterman, M. Hayashida, C. P. O'Brien, *ibid.*, p. 876; H. Sass, M. Soyka, K. Mann, W. Zieglgansberger, *ibid.* **53**, 673 (1996).
35. J. R. Volpicelli, M. A. Davis, J. E. Olgin, *Life Sci.* **38**, 841 (1986); R. Spanagel, S. M. Hoelter, K. Allingham, R. Landgraf, W. Zieglgansberger, *Eur. J. Pharmacol.* **305**, 39 (1996); C. J. Heyser, G. Schulteis, P. Durbin, G. F. Koob, *Neuropsychopharmacology*, in press.
36. D. Smith, personal communication.
37. J. M. Murphy, W. J. McBride, L. Lumeng, T.-K. Li, *Pharmacol. Biochem. Behav.* **26**, 389 (1987).
38. J. C. Crabbe and J. K. Belknap, *Trends Pharmacol. Sci.* **13**, 212 (1992); L. H. Gold, *Behav. Pharmacol.* **7**, 589 (1996); H. W. D. Matthes *et al.*, *Nature* **383**, 819 (1996).
39. M. J. Kreek, in *Psychopharmacology: The Third Generation of Progress*, H. Y. Meltzer, Ed. (Raven Press, New York, 1987), pp. 1597–1604.
40. P. V. Piazza and M. Le Moal, *Annu. Rev. Pharmacol. Toxicol.*, **36**, 359 (1996).

41. V. Deroche *et al.*, *Brain Res.* **598**, 343 (1992); P. V. Piazza and M. Le Moal, *Brain Res. Rev.*, in press.
42. C. R. Schuster and T. Thompson, *Annu. Rev. Pharmacol. Toxicol.* **9**, 483 (1969); M. E. Carroll, S. T. Lac, S. L. Nygaard, *Psychopharmacology* **97**, 23 (1989).
43. P. V. Piazza, J.-M. Deminiere, M. Le Moal, H. Simon, *Science* **245**, 1511 (1989).
44. S. Cabib and S. Puglisi-Allegra, *Psychopharmacology*, **128**, 331 (1996); A. R. Cools and M. Gingras *Pharmacol. Biochem. Behav.*, in press.
45. P. Sterling and J. Eyer, in *Handbook of Life Stress Cognition and Health*, S. Fisher and J. Reason, Eds. (Wiley, New York, 1988), pp. 629–649; B. S. McEwen and E. Stellar, *Arch. Intern. Med.* **153**, 2093 (1993).
46. D. A. Bindra, *A Theory of Intelligent Behavior* (Wiley, New York, 1976).
47. M. J. Ellenhorn and D. G. Barceloux, *Medical Toxicology: Diagnosis and Treatment of Human Poisoning* (Elsevier, New York, 1988).
48. C. R. Cloninger, M. Bohman, S. Sigvardsson, *Arch. Gen. Psychiatry* **38**, 861 (1981).
49. G. Schulteis, C. J. Heyser, G. F. Koob, *Psychopharmacology* **129**, 56 (1997).
50. The concept of limited energy within a hedonic system can be traced at least as far back as Carl Jung, where the psyche was regarded as a relatively closed system. This limited energy was expressed by the term "libido," which basically described a general life instinct or psychic energy. Jung wrote, "Since our experience is confined to relatively closed systems, we are never in a position to observe an absolute psychological entropy, but the more the psychological system is closed off, the more clearly is the phenomenon of entropy manifested (a system is absolutely closed when no energy from outside can be fed into it)" [C. G. Jung, *The Structure and Dynamics of the Psyche* (translation from *Über die Energetik der Seele* [On the Driving Force of the Soul], vol. 8 of *Über psychische Energetik und das Wasen der Traume* [On Psychological Energy and the Meaning of Dreams] (Rascher, Zurich, 1948)) (Princeton Univ. Press, Princeton, NJ, ed. 2, 1969)].
51. The theological system of Calvin and his followers is marked by a strong emphasis on the sovereignty of God, the depravity of humankind, and the doctrine of predestination. Calvinism is characterized by a strict, disciplined lifestyle where morality is tantamount and there is a strong sense of church unity. Calvinists, and later Puritans, with regard to personal life, demanded of themselves a reformation of character, the rejection of idle recreations and vain display, and sober, obedient godliness [S. E. Ahlstrom, *A Religious History of the American People* (Yale Univ. Press, New Haven and London, 1972].
52. G. Schulteis, A. Markou, M. Cole, G. F. Koob, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 5880 (1995).
53. G. Schulteis, A. Markou, L. Gold, L. Stinus, G. F. Koob, *J. Pharmacol. Exp. Ther.* **271**, 1391 (1994).
54. V. Deroche, M. Marinelli, M. Le Moal, P. V. Piazza, *ibid.* **281**, 1401 (1997).
55. P. V. Piazza *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 8716 (1996).
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Molecular and Cellular Basis of Addiction

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Drug addiction results from adaptations in specific brain neurons caused by repeated exposure to a drug of abuse. These adaptations combine to produce the complex behaviors that define an addicted state. Progress is being made in identifying such time-dependent, drug-induced adaptations and relating them to specific behavioral features of addiction. Current research needs to understand the types of adaptations that underlie the particularly long-lived aspects of addiction, such as drug craving and relapse, and to identify specific genes that contribute to individual differences in vulnerability to addiction. Understanding the molecular and cellular basis of addictive states will lead to major changes in how addiction is viewed and ultimately treated.

Addiction is a complex phenomenon with important psychological and social causes and consequences. However, at its core, it involves a biological process: the effects of repeated exposure to a biological agent (drug) on a biological substrate (brain) over time. Ultimately, adaptations that drug exposure elicits in individual neurons alter the functioning of those neurons, which in turn alters the functioning of the neural circuits in which those neurons operate. This leads eventually to the complex behaviors (for example, dependence, tolerance, sensitization, and craving) that characterize an addicted state (*1*, *2*).

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A critical challenge in understanding the biological basis of addiction is to account for the array of temporal processes involved (Fig. 1). Thus, the initial event leading to addiction involves the acute action of a drug on its target protein and on neurons that express that protein. These actions are now well understood and will not be reviewed here (*1*, *2*). Rather, this review focuses on the molecular and cellular adaptations that occur gradually in specific neuronal cell types in response to chronic drug exposure, particularly those adaptations that have been related to behavioral changes associated with addiction. We focus on opiates and cocaine, not only because they are among the most prominent illicit drugs of abuse, but also because considerable insight has been gained into the adaptations that underlie their chronic actions. As will be seen, the relatively short-lived adaptations that contribute to relatively transient features of addiction (for example, somatic and motivational withdrawal symptoms and changes in drug sensitivity) are becoming increasingly understood. In contrast, a major need for future research is to identify and characterize more long-lived adaptations that underlie aspects of addiction (for example, craving and relapse) and can persist for a lifetime.

Up-Regulation of the cAMP Pathway

The best established molecular adaptation to chronic drug exposure is up-regulation of the adenosine 3′,5′-monophosphate (cAMP) pathway, a phenomenon first discovered in cultured neuroblastoma × glioma cells (*3*) and later demonstrated in neurons (*4*) in response to repeated opiate administration. Acute opiate exposure inhibits the cAMP pathway in many types of neurons in the brain (*5*), whereas chronic opiate exposure leads to a compensatory up-regulation of the cAMP pathway in at least a subset of these neurons. This up-regulation involves increased concentrations of adenylyl cyclase, cAMP-dependent protein kinase A (PKA), and perhaps other components of this signaling pathway. Up-regulation of the cAMP pathway would oppose acute opiate inhibition of the pathway and thereby would represent a form of physiological tolerance; upon removal of the opiate, the up-regulated cAMP pathway would become fully functional and contribute to features of dependence and withdrawal (*3*, *4*).

There is now direct evidence to support this model in neurons of the locus coeruleus, the major noradrenergic nucleus in the brain. These neurons normally regulate attentional states and activity of the auto-