

Cocaine Addiction: Psychology and Neurophysiology

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Cocaine was considered incapable of producing dependence in 1980 but was recently proclaimed the drug of greatest national health concern. Recent clinical and pre-clinical investigations demonstrate that cocaine produces unique abuse and withdrawal patterns that differ from those of other major abused drugs and suggest that long-term cocaine abuse produces neurophysiological alterations in specific systems in the central nervous system that regulate the capacity to experience pleasure. It will be necessary to develop clinically pertinent research models before these findings can be considered definitive, but these evolving ideas have already led to applications of promising experimental treatments for cocaine abuse.

ADDICTION TO COCAINE DOES NOT CAUSE GROSS PHYSIOLOGICAL withdrawal symptoms. However, the addictive consequences of cocaine use have forced reconsideration of the importance attributed to "classic" drug abuse constructs, such as physiological withdrawal, tolerance, and physical dependence, in drug and alcohol addiction. These constructs are based on easily quantitated gross physiological alterations in parameters such as heart rate or blood pressure and on easily observed symptoms of physical illness. Their central position in drug abuse theory and research, although questioned, has been unchanged for decades; drug dependence has thus largely been considered an avoidance of physical discomfort on withdrawal.

Pharmacological agents have been developed that reverse the gross physiological withdrawal symptoms produced by benzodiazepines, alcohol, and opiates. However, these agents, fully assessed in recent clinical treatment trials, have not solved the problem of addiction to these drugs. The facts that cocaine produces no gross physiological withdrawal symptoms and that, in withdrawal from other abused drugs, agents reversing such symptoms show limited efficacy, demonstrate that subjective experiences or symptoms other than physiological discomfort are crucial in addiction to cocaine and to other substances of abuse.

Clinical and preclinical investigators are now exploring how psychological symptoms in drug withdrawal, particularly unpleasant mood states and cravings for drug euphoria, maintain chronic drug addiction. Such symptoms may be mediated by neurophysiological adaptations that are attributable to repeated perturbations of the central nervous system (CNS) by abused drugs. In cases where these adaptations occur in brain systems that regulate only processes lacking physical expression, as appears to be the case with cocaine, addiction may have been erroneously considered as purely "psychological" rather than "physiological" and had erroneously been

presumed to pose less severe treatment problems. The perception that cocaine produced purely a psychological problem wrongly implied that it was appropriate to limit treatment to psychological therapies and suggested there was no role for neurophysiological interventions with pharmacological agents. These drawbacks of prior "classic" tenets in the drug abuse field has recently led the World Health Organization to discard these terms in favor of the more physiologically precise term "neuroadaptation" (1) and has led the American Psychiatric Association to define drug dependence by using behavioral criteria, rather than only physiological criteria (2).

The epidemic of cocaine abuse may therefore provide one positive legacy—forced recognition of the complexity of substance abuse and new conceptualizations of and research on addiction. In this article, I review the recent concordance of clinical and preclinical findings about long-term cocaine exposure that suggest cocaine causes a neurophysiological addiction. Corresponding advances in the treatment of cocaine abuse are noted, but these are discussed fully elsewhere (3, 4). Further, this article will describe the methodological limitations of current preclinical and clinical research to illustrate where conceptual or technical methodological advances are now a prerequisite to systematic advancement of research, theory, and treatment of the addictions.

The Clinical Characteristics of Cocaine Addiction

We are in the largest cocaine abuse epidemic in history. In the United States alone, one to three million cocaine abusers are estimated to be in need of treatment (5), or up to six times the number of heroin addicts. In the 1890s, cocaine use also surged and was considered safe by clinicians as illustrious as Sigmund Freud (6). Use declined after its dangers became well known (7). This recurred in the 1920s. In the early 1950s and late 1960s, abuse of the similar stimulants, amphetamine and methamphetamine, resulted in the same pattern (8). In 1980, cocaine was again considered a safe, nonaddicting euphoriant (9). Historical descriptions of cocaine dependence were dismissed as exaggerations similar to marijuana reports from earlier eras. Clinical research on cocaine abuse that used systematic and objective techniques did not exist, and this led to the miscomprehension that cocaine dependence did not exist. Cocaine use then exploded. Almost one of two Americans between 25 and 30 years of age has tried cocaine. A powerful new route of administration has appeared; cocaine smoked as the free base, also called "crack," is as addictive as intravenous injection, without the stigma or infectious dangers of injection (10).

Individuals who are in treatment for cocaine abuse report that 2 to 4 years intervene between the initial exposure to cocaine and the development of addiction (11); this interval has delayed reports of cocaine's adverse effects at the beginning of epidemics and, combined with reports of apparently controlled initial use, promotes

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illusions of safety. Early in the course of cocaine epidemics, the public, scientists, respected texts, and astute clinicians have all fallen victim to this illusion, thus enabling the repeated emergence of cocaine abuse.

Psychological effects of cocaine: initial use. In both reports from individuals addicted to cocaine and human laboratory investigations (in which cocaine is administered to nonaddicted cocaine users), cocaine initially induces profound subjective well-being together with alertness (6, 7, 12, 13). The fundamental effect of cocaine is the magnification of the intensity of almost all normal pleasures. The environment takes on intensified but nondistorted qualities. Emotions and sexual feelings are enhanced (6, 13). Self-confidence and self-perceptions of mastery increase, so anxiety is initially decreased. Social inhibitions are reduced, and interpersonal communication is facilitated. Satiation of appetite occurs, so pleasures associated with eating are not enhanced (11, 12).

Human laboratory studies of cocaine's effects are more reliable than retrospective self-reports by cocaine users, but they are seriously limited as aids in understanding cocaine abuse because there are multiple disparities between the methods used in such experiments and the characteristics of actual street cocaine use. Maximum individual laboratory doses are 10% of the maximum doses typically reported by street abusers (12). The maximum duration of administration in human experiments is 5 hours (14), compared to street binges lasting as long as 200 hours. Cocaine abusers usually coadminister other drugs (alcohol, heroin, and marijuana) to decrease unpleasant components of the cocaine experience, such as anxiety, that admix with euphoria. The effects of coadministration of these drugs, of their relative dosages, and of varying the time patterns of their administration have not been studied. Further, because administration of cocaine to a cocaine abuser in need of treatment has been considered unethical, the subjects in such studies are not in need of treatment for cocaine abuse, have less severe histories of cocaine abuse, and may often instead have substantial histories of abuse of other substances. These facts raise the possibilities that any neuroadaptation pertinent to cocaine dependence is not present, or that neuroadaptation to other abused substances might be present, or both. Finally, the effects of nonpharmacological factors that interact with the effects of cocaine have been largely ignored. Variations in the environmental context of cocaine administration, such as familiarity with the administration environment, the spectrum and pleasantness of available activities, degree of interpersonal isolation, degree of perceived safety, presence or difficulty of tasks, perceived medical risk, and many others may all affect cocaine's use and effects but have not been studied. Such studies are fundamental. For example, it is unknown whether the distraction that is required for reporting the subjective effects of cocaine to investigators might substantially alter the experience of cocaine euphoria.

Psychological effects of cocaine: addiction and dependence. On the basis of National Institute of Drug Abuse estimates, only about 10 to 15% of those who initially try cocaine intranasally become abusers. Some individuals who experiment with cocaine cease use immediately, typically describing overwhelming anxiety rather than euphoria as cocaine's main effect. Some who do experience intensified euphoria cease use because of extreme expense or unavailability. Others, before addiction is fully developed, fear imminent loss of self-control over cocaine use and are able to cease use.

Individual differences in the progression to addiction could provide crucial insights for prevention and treatment. However, reliable predictors of later heavy abuse have not been found in light cocaine users who have not yet developed addiction; a cocaine "addictive" personality has not been identified; and no objective, systematic assessments of the natural longitudinal course of cocaine

use and abuse exist (3).

As cocaine addiction develops, a transition to high-dose, long-duration bingeing occurs, in which the intensely pleasurable effects are experienced alone, and increasingly apparent negative contingencies go unrecognized (3, 6, 10, 15). Users readminister cocaine every 10 to 30 min. Such compulsive, uncontrolled binge use begins when availability and dosage escalate (for example, as a result of increased funds or improved supply sources) or when a switch to rapid, higher intensity administration routes occurs (from intranasal use to smoking or intravenous injection) (3, 15-17). During such binges, there are numerous periods of extreme euphoria, and vivid memories are formed that are later contrasted with current dysphorias to produce cocaine craving (3, 16). Several days of abstinence often separate binges; users average one to seven binges per week, each lasting from 4 to 24 hours (3, 16). Unlike the case for alcohol or opiate users, the absence of a daily use pattern in a cocaine user does not indicate decreased impairment, and it may indicate the opposite (3).

Continuous, rapid, cocaine self-administration also occurs in animal experiments in which unlimited access to intravenous cocaine is provided (12). The animals die within 14 days. If access is limited, an animal will press a lever thousands of times for a single cocaine dose (12). Human cocaine addicts report that virtually all thoughts are focused on cocaine during binges; nourishment, sleep, money, loved ones, responsibility, and survival lose all significance (3, 16). Supplies of cocaine are drawn on until they are exhausted. Limitations on drug access, including the high price of cocaine and legal limitations on distribution, regulate human cocaine use and may prevent human cocaine use from more frequently mimicking animal free-access experiments in producing death. A low-intensity parallel to early, controlled use in humans has not been described in animal self-administration studies, probably because most self-administration experiments in animals utilize large boluses and intravenous administration, bypassing an initial phase of low-intensity use and the binge transition (3).

Cocaine Abstinence Symptoms

A triphasic pattern of symptoms characterizes the response to abstinence from cocaine (16); this pattern dispels the perception that cocaine use produces no withdrawal. This abstinence sequence, initially described on the basis of clinical observations in 30 outpatients, has been verified in one large-scale outpatient study and some (but not all) assessments in hospitalized cocaine abusers, as well as in animal models and positron emission tomographic (PET) studies in humans (18). The symptoms of cocaine abstinence are more complex and subtle than those previously associated with drug withdrawal, and researchers cannot be certain of the characteristics of cocaine abstinence until methodological obstacles, delineated below, can be surmounted. Cocaine abstinence is shown schematically in Fig. 1.

Phase one—crash. Immediately after cessation of a cocaine binge, there is a "crash" of mood and energy (3, 10, 16). Cocaine craving, depression, agitation, and anxiety then rapidly intensify, and, in over half of abusers seeking treatment, suspiciousness and paranoia are prominent (14, 19). During the next 1 to 4 hours, cocaine craving decreases and is supplanted by mounting exhaustion and craving for sleep; further use is then often strongly rejected, unlike in the parallel situation after several hours of opiate, sedative, or alcohol withdrawal (3, 16). Abusers administer marijuana, sedatives, opiates, or alcohol to induce sleep, and after sleep begins, they experience intense hypersomnolence, with electroencephalographic changes characteristic of sleep deprivation (20). During brief awak-

enings, hyperphagia occurs. The hypersomnolence can last several days, after which mood normalizes.

The crash has been confused with withdrawal (8, 10), but the crash parallels an alcohol hangover, not the withdrawal associated with chronic opiate or alcohol administration (3), and although crash symptoms prolong cocaine binges, they do not maintain long-term cocaine abuse.

Phase two—withdrawal. In addition to cocaine, continued use is induced by a protracted dysphoric syndrome—including decreased activation, anxiety, lack of motivation, and boredom, with markedly diminished intensity of normal pleasurable experiences (anhedonia)—that emerges shortly (0.5 to 4 days) after the crash. This hedonically limited existence, when contrasted to memories of cocaine-induced euphoria, induces severe cocaine cravings, resumption of use, and unceasing cycles of recurrent binges (3, 16). Because it is directly related to craving and resumption of use, this withdrawal phase parallels withdrawal from other abused substances, except that there is an absence of gross physiological changes (16). These symptoms are far more subtle than those of the crash and went unrecognized by early observers. They are not constant or severe enough to meet the criteria for major psychiatric mood disorders.

The existence of a withdrawal phase is indicated by broad clinical and preclinical observation and consensus (3, 15, 18). However, precise and objective quantitation of anhedonia and similar dysphoric symptoms is problematic. Available psychiatric and psychological rating scales are not sensitive to these subtle mood components. For example, no scale or technique assessing anhedonia has been validated in human substance abusers (21). Further, quantitation of anhedonia requires interactive assessment with a pleasurable probe because anhedonia is the absence of an appropriate mood response to a pleasurable event. In addition, there are extensive individual differences in the perception of what stimuli are pleasurable: there are few or no events that can serve as plausible human research tools and that uniformly induce pleasure. In animals, however, elegant methods involving behavioral or electrophysiological responses to electrical, pharmacological, or behavioral stimulation have been developed that allow study of reward responses (reviewed below), and complementary preclinical data exist to support the hypothesis that impairment of reward responses occurs after chronic cocaine abuse.

There are established and validated measurement techniques for anxiety, unlike for anhedonia. Experimental cocaine administration

in animal models and anxiety inventory ratings in humans have confirmed the slightly delayed emergence of anxiety during cocaine withdrawal (18).

Cocaine abusers desiring to cease use are cognizant, when in withdrawal, of the adverse consequences of continued cocaine use. They are usually able to transiently withstand this anhedonic dysphoria, until they are presented with a conditioned cue. The cue superimposes a second, more transient dimension of craving (evoked craving) on anhedonic craving, and, most often, cocaine use then resumes. Conditioned cocaine craving is described as pulsatile, lasting only minutes or hours. Cocaine and the amphetamines are the most potent reinforcing agents known, and as such they produce intense classical and operant conditioning (12). Such cravings appear after the appearance of varied, idiosyncratic objects or events that were temporally paired with prior cocaine intoxications, and these appearances are experienced as partial memories of cocaine euphoria. Cues can include mood states (positive as well as negative), specific persons, locations, events or times of year, mild alcohol intoxication, interpersonal strife previously soothed by cocaine euphoria, or abuse objects (for example, money, white powder, glass pipes, mirrors, syringes, and single-edged razor blades) (3, 16, 22).

Initiation of a cocaine binge thus depends on an interaction between drug availability, environmental stimuli (conditioned cues), and the withdrawal status of the dependent abuser. The time course of binge resumption fluctuates within and between cocaine-dependent individuals, to an extent much greater than in opiate or alcohol withdrawal, and depends on the weight of these three factors. Manipulation of these factors has thus become the focus of initial medical and societal interventions to control cocaine addiction. Recent treatment advances focus on decreasing withdrawal dysphoria pharmacologically or on extinguishing conditioned craving by using graded exposure to cocaine, and public policy advances in law enforcement could decrease availability of cocaine.

Although the interplay of these factors has been well described in cocaine-dependent humans, the interactions of these factors have not been studied in preclinical experiments in animals. Excellent models exist for each of the factors. Investigators could model availability of cocaine by changing the parameters of work (change in pattern or amount of lever-pressing required for a stimulant dose) or by producing impediments to access (delivery of aversive stimuli). Conditioned associations, created by pairing of experimental events with cocaine or amphetamine administrations, have been studied, isolated from these other factors, quite extensively. Finally, withdrawal status could be modeled by regulation of the chronicity, administration route, and pulse pattern of cocaine administration, and craving can be modeled by assessment of avidity of responding (point of response cessation after reward ceases) and frequency of choosing alternative nondrug reinforcers (food, sex, social interaction), after long-term cocaine treatment in animals that precisely duplicates human use patterns.

Thus, the cocaine disease process could be precisely reconstructed in animals, particularly regarding administration patterns and aversive stimuli, but animal models designed to mimic human cocaine administration characteristics have not been used. This is ironic because the unavailability of precise animal models that impedes rapid advances in other psychiatric and medical disorders is avoidable in studies of cocaine abuse. For example, potential pharmacotherapies targeted at conditioned cocaine craving have not appeared in clinical or preclinical research. Such treatments are nonetheless plausible and could be screened by assessment of the effect of pharmacological agents on cocaine-seeking behavior that has been linked to conditioned cues in animals treated with cocaine for long periods of time in a binge pattern like that seen in humans. Similarly,

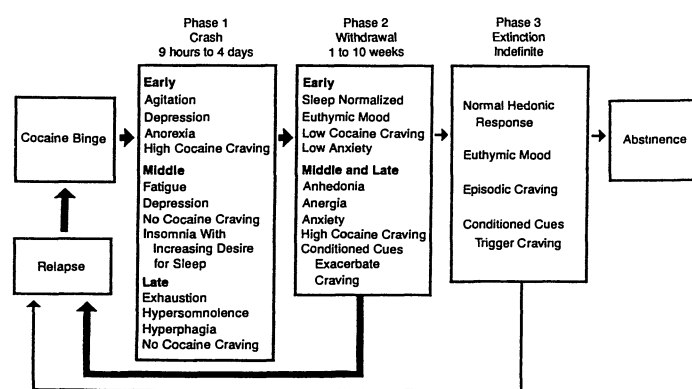


Fig. 1. Cocaine abstinence phases. Duration and intensity of symptoms vary on the basis of binge characteristics and diagnosis. Binges range in duration from under 4 hours to 6 or more days. High cocaine craving in phase 1 usually lasts less than 6 hours and is followed by a period of noncraving with similar duration in the next subphase (middle phase 1). Substantial craving then returns only after a lag of 0.5 to 5 days, during phase 2. [Reprinted from (16) with permission, *Arch. Gen. Psychiatry*]

the relative importance of conditioned craving and withdrawal craving at varied stages and degrees of abstinence, which is currently limited to clinical conjecture, could be modeled. Differential and specific treatment effects are also likely to appear according to the stages and degrees of abstinence at the time a treatment technique is applied (for example, isolation from or exposure to cocaine availability, and pharmacotherapy at the time withdrawal anhedonia is present). Optimal intervention timing and interactions between treatments could be precisely modeled and rapidly evaluated. Finally, public policy could be based on experimental findings modeled in animals, but it is not. For example, the effect of decreasing the availability of cocaine on increasing work for cocaine (the human equivalent to this work is often criminal activity) could predict how the crime rate would change after an increase in cocaine prices. At present, vast government expenditures occur (on the basis of the presumption that increased price would decrease use and crime), in the absence of guidance from such plausible experiments.

If cocaine abusers sustain abstinence, anhedonic symptoms lift within 2 to 12 weeks (16). Animal studies show that behavioral depression occurs after stimulant withdrawal for a similar time period (23). On the basis of clinical observations, symptom severity and duration depend on the intensity of the preceding months of chronic abuse and on the presence of predisposing psychiatric disorders, which amplify withdrawal symptoms (16). Conversely, in infrequent cocaine users without psychiatric disorders, withdrawal may not occur. High-intensity binge cocaine use and coinciding neuroadaptation may be required before withdrawal occurs.

Phase three—extinction. After resolution of withdrawal anhedonia, intermittent, conditioned cocaine craving can still emerge (16) months or even years after the last cocaine use. Lasting cocaine abstinence depends on experiencing intermittent, conditioned craving without relapse. The previous consistent pairing of cues with cocaine euphoria then does not occur, and craving is gradually extinguished (16, 22). Relapse caused by classically conditioned craving and withdrawal has been described in opiate and nicotine withdrawal. In cocaine dependence, however, conditioned craving may be more intense than in other addictive disorders. This is not surprising because cocaine is such a powerful reinforcer in animal models and because of the relation between strength of reinforcement and magnitude of classical conditioning.

Short-Term Neurochemical Actions of Cocaine

Cocaine and the amphetamines are thought to produce pleasure or reward by increasing neurotransmission in mesolimbic or mesocortical dopaminergic tracts, or both, in the brain (24). In animals, electrical self-stimulation of these pathways produces reward-seeking behavior that mirrors that of cocaine self-administration. Both electrical self-stimulation of these pathways and cocaine increase extracellular dopamine concentration in brain nuclei that control reward behavior. Lesions in these pathways block cocaine effects, and dopamine receptor blockers attenuate cocaine effects (25). Whether cocaine also directly influences efferent or afferent connections is less clear.

Cocaine inhibits reuptake of the neurotransmitters norepinephrine and serotonin, as well as of dopamine. It binds to the dopamine transporter labeled by mazindol and to imipramine binding sites on serotonergic neurons (26). It is a local anesthetic (26) and also increases catecholamine receptor sensitivity (27). In contrast to abused substances like heroin, cocaine does not directly activate enkephalinergic receptors, but may indirectly influence these sys-

tems. Cocaine also affects neurotransmission in histamine, acetylcholine, and phenethylamine pathways.

None of these neurotransmitter actions are solely responsible for cocaine euphoria because each is also produced by other pharmacological agents that do not produce euphoria, are not self-administered by animals, and are not abused by humans (3). Thus, although the rewarding properties of cocaine clearly require activation of dopaminergic systems, the molecular mechanisms involved and whether activation is due only to direct cocaine effects on dopaminergic neurons or to simultaneous collateral actions on other neurotransmitters is uncertain (3, 28). Several lines of evidence support the hypothesis that a simultaneous interaction between catecholamine and serotonergic systems is fundamental to cocaine reward and euphoria. Cocaine and other abused stimulants, such as the amphetamines and methylphenidate, have numerous structural and neuropharmacological dissimilarities, but all produce, by means of neurotransmitter reuptake inhibition, activation of dopaminergic and noradrenergic pathways associated with mood and activation of serotonergic systems associated with mood and arousal. Manipulations of serotonergic systems modulate the reward potency of both cocaine and amphetamine in animals, and agents that activate dopaminergic or noradrenergic systems, or both, but are devoid of strong serotonergic activity (benztropine, trihexyphenidyl, nomifensine, L-dopa/carbidopa) are neither intensively abused by humans or, when administered systemically rather than directly into the CNS, avidly self-administered by animals (29). Pure serotonin agonists and antagonists lacking acute dopaminergic activity, including those with selective activity at specific serotonin receptor subtypes, also do not produce reward or abuse. Hence, the author proposes that augmentation of the effects of dopamine reuptake blockade probably occurs by way of other inputs (serotonergic or others) to dopaminergic reward pathways to produce sufficient dopaminergic activation to cause stimulant euphoria. For example, serotonergic synapses exist on the cell body of dopaminergic neurons in the midbrain (A10) that may, in turn, regulate activation thresholds in reward cells. Cocaine-induced serotonin reuptake inhibition could magnify cocaine-induced perturbations in the dopaminergic reward system to induce euphoria. If so, blockade or perturbation of serotonin or other augmenting systems might block cocaine effects while minimally influencing normal reward transmission and, unlike the dopamine receptor-blocking neuroleptics, averting exacerbation of anhedonia.

Neuroadaptation to Long-Term Cocaine Abuse

The response of the nervous system to persistent, drug-induced neurochemical perturbation is a compensatory adaptation in the perturbed systems. Dysregulation follows adaptation when the drug is not present. Despite this, until recently it had been assumed that neuroadaptation does not occur in cocaine abuse. Gawin, El-kinwood, and Kleber have hypothesized that high-dose cocaine use over long periods of time generates sustained neurophysiological changes in brain systems that regulate only psychological processes, particularly hedonic responsivity or pleasure (3, 16). Changes in these neurophysiological systems produce a true physiological addiction and withdrawal, but one whose clinical expression appears solely psychological (3).

Intracranial electrical self-stimulation (ICSS) of brain reward sites in animals provides a model for human pleasure. Chronic cocaine and amphetamine administration appears to decrease ICSS reward indices and to increase the threshold voltage required to elicit ICSS

in dopaminergic reward areas such as the nucleus accumbens (24). These ICSS decrements imply that brain reward regions affected by cocaine are subsensitive or down-regulated. They are consistent with clinical observations of protracted anhedonia in abstinent cocaine abusers and with behavioral depression after cocaine use in animals.

The neurophysiological dysregulations that would be consistent with these ICSS data have not been clearly established, but could take place at several sites. Central dopaminergic, α -adrenergic, and β -adrenergic receptor supersensitivity has been demonstrated after long-term cocaine administration in animals (30). Receptor alterations could produce ICSS decrements in animals and anhedonia in humans (30). It has only recently been possible to differentiate presynaptic and postsynaptic receptor changes and D1, D2, D3, and D4 dopamine receptors. A primary effect of decreased dopaminergic reward transmission would produce a secondary increase in postsynaptic receptor sensitivity. Disproportionate D2 autoreceptor supersensitivity (that is, greater functional autoreceptor supersensitivity than postsynaptic D2 receptor supersensitivity) would decrease dopaminergic neurotransmission. Such changes have been demonstrated in animals with continuous but not intermittent long-term administration of cocaine and amphetamine (31). Alternatively, other feedback mechanisms could influence firing and activation thresholds, or other parameters of transmitter release, in dopaminergic reward nuclei. These include possible neurotoxic degeneration of dopaminergic reward neurons (3, 32). D1 receptor-mediated feedback innervation to the cell bodies of reward neurons, and multiple possible feedback loops involving serotonergic, noradrenergic, enkephalinergic, and GABAergic synapses (GABA, γ -aminobutyric acid), among others. Pharmacological interventions at each of these sites influence cocaine administration in preliminary preclinical or clinical reports. The predominant pharmacological treatment thus far investigated in therapy for cocaine addiction (the tricyclic antidepressants) has multiple effects that are opposite to those of long-term cocaine use: applied on a long-term basis, the antidepressants increase ICSS reward sensitivity, neuronal firing rates, and synaptic dopamine concentrations in dopaminergic reward neurons (3, 30). They may also induce dopaminergic autoreceptor subsensitivity, and they may have antianhedonic effects in unipolar depression (3, 30).

The appropriateness of generalization from long-term cocaine administration studies in animals to human cocaine withdrawal anhedonia is uncertain. Almost all animal research on long-term administration of cocaine or other stimulants has used drug administration paradigms that do not reflect human abuse patterns. For example, these animal studies usually utilize daily intraperitoneal administration, producing a slowly increasing single peak in dopaminergic facilitation each day, and minimal sleep disruption. This does not coincide with the multidose binges, perturbed diurnal cyclicity, and multiple-day cocaine-free intervals characteristic of human abusers seeking abstinence. Long-term cocaine administration in animal studies varies in duration from 5 days to 3 months and may not have consequences similar to multiple years of human abuse. Further, it is unclear how species differences in life-span should be interpreted in extrapolation of these studies to humans.

Neurochemical studies in cocaine abusers seeking treatment are also limited. Several investigations have assessed peripheral neuroendocrine and neurotransmitter metabolite indices of central dopaminergic functioning in treatment-seeking cocaine abusers. Such studies are potentially confounded by multiple sources: concurrent medical or psychiatric disorders, the intensity and time course of antecedent cocaine use, other drugs abused, questionable reliability of details of self-reports, diet, duration of abstinence, and genetic heterogeneity, among many others. The complexities presented by differences in antecedent history can, at present, be

resolved only by studies of long-term cocaine administration in animals in which these variables are systematically regulated.

Despite such limitations, neurochemical studies based on peripheral indices of dopaminergic functioning and electroencephalographic studies in street abusers suggest that neuroadaptation occurs in street cocaine abuse (18, 20, 33). Both homovanillic acid (HVA), the principle metabolite of dopamine in humans, and the neurohormone prolactin (inhibited by tuberoinfundibular dopamine release) have been assessed. Basal prolactin and HVA concentrations in cocaine abusers are either unchanged or reflect decreased dopaminergic functioning (34). However, three studies now indicate that transiently increased dopaminergic functioning is associated with resurgence of craving for cocaine (18, 33). This is consistent with microdialysis studies in animals indicating that conditioned cues and nondrug stimuli that indicate craving (exposure of male rodents, without access, to sexually receptive females) are associated with increased dopamine release, of substantially less magnitude than that caused by cocaine, in the nucleus accumbens (35). It is possible that such fluctuations in dopaminergic activity occur broadly enough to be reflected in less sensitive peripheral assessments in humans.

In vivo imaging of human brain functioning can directly measure metabolism and neurophysiology in cocaine abusers (18). The spatial and temporal resolution of PET scanning, single photon emission computerized tomography, magnetic resonance spectroscopy, and methods of assessing regional cerebral blood flow appear to be insufficient for precise demonstration of alterations in reward function in human abusers. For example, diminished reward function could occur only in the nucleus accumbens, which is beyond the spatial resolution of current methods; and the period of craving that follows a conditioned cue may be associated with very brief activation or deactivation of reward pathways that may not be detectable because of the relatively lengthy acquisition time of these imaging techniques. Simple practical problems also exist. Because of the unpredictable time course of cocaine abstinence symptoms, imaging cannot be scheduled to coincide with specific clinical states, and keeping equipment and personnel at ready is implausible.

Recovery and Treatment

Data from treatment programs using different therapeutic approaches indicate that outpatient cocaine abuse treatment can be successful. From 30 to 90% of abusers remaining in outpatient treatment programs cease cocaine use (36). Samples vary widely in degree of abuse severity, psychosocial resources, route of administration, and magnitude and pattern of cocaine and other drug exposure, so they are not readily comparable. Further, rigorous design is usually lacking, so little evidence exists to suggest that any one treatment approach is superior (3). Also, despite superficial differences, strong commonalities characterize all current treatment strategies. Initial efforts focus on retaining the abuser in treatment and disrupting the cycles of binges; subsequent efforts focus on relapse prevention (3).

There is controversy regarding the relative therapeutic value of, and indications for, most components of cocaine abuse treatment. These include, but are not limited to, hospital versus outpatient cocaine abuse treatment; types of treatment techniques; use, selection, dosage, or duration of adjunctive medication; lengths of isolation from and rapidity of latter immersion in the environment in which cocaine is available; and most other variables in treatment design. These areas require assessment in controlled, random-assignment treatment studies.

Recent double-blind comparisons of medication treatment and abstinence initiation in outpatients have demonstrated that hetero-

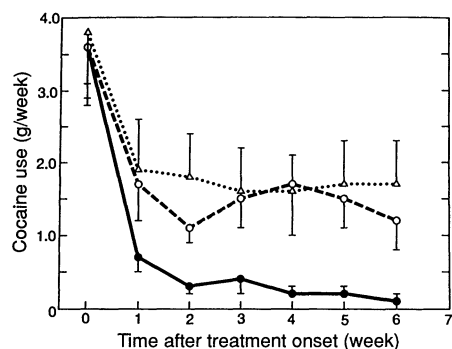


Fig. 2. Desipramine facilitation of initial cocaine abstinence. End-point analysis of reported cocaine use (grams) during treatment of outpatient cocaine abusers with desipramine hydrochloride (2.5 mg per kilogram of body weight per day, $n = 24$, solid line), lithium carbonate (17.5 mg/kg, $n = 24$, dashed line), or placebo ($n = 24$, dotted line). [Reprinted from Gawin *et al.* (37) with permission, *Arch. Gen. Psychiatry*]

cyclic antidepressants (desipramine and imipramine), which do not produce dependence or addictive use patterns, diminish cocaine use and craving and improve initial treatment outcome in the first months of treatment (Figs. 2 and 3) (4, 37). Multiple uncontrolled reports also exist of decreases in craving induced by other agents that are hypothesized to normalize reward function, and multiple double-blind trials of similar pharmacological treatment for cocaine craving are in progress. Efforts to block the effects of cocaine appear less promising. Dopamine blocking agents may block cocaine effects, but apparently do so only at doses that so markedly amplify anhedonia that such treatment is counter-therapeutic (28, 38). Reports of other agents that may decrease self-administration of cocaine in animals have been difficult to interpret. Buprenorphine, for example, was reported to diminish cocaine administration in primates by presumed decreases in reward potency (39). However, increases in reward also diminish frequency of administration in animals, and rodent studies are consistent with buprenorphine augmentation, rather than blockage, of the effects of cocaine (40).

The feasibility of systematic, controlled psychotherapy research for cocaine abuse is demonstrated by promising assessments of systematic desensitization of cues eliciting conditioned cocaine craving, but only preliminary clinical trials have appeared (43). In-depth studies of the outcome of systematic desensitization are in progress, as are studies contrasting psychotherapies with and without pharmacotherapies that are similar to prior studies of severe depression treatment in non-drug users.

Conclusions

Cocaine addiction has evolved within one decade from a virtually nonexistent problem to a complexly regulated disorder with interwoven environmental, psychological, and neurophysiological com-

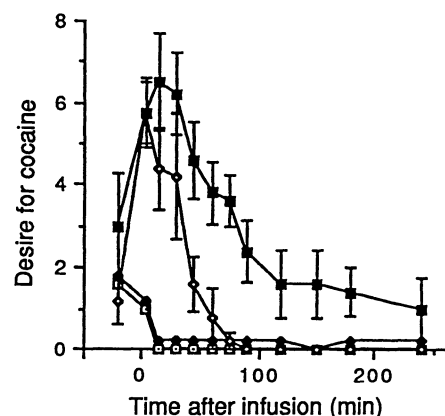


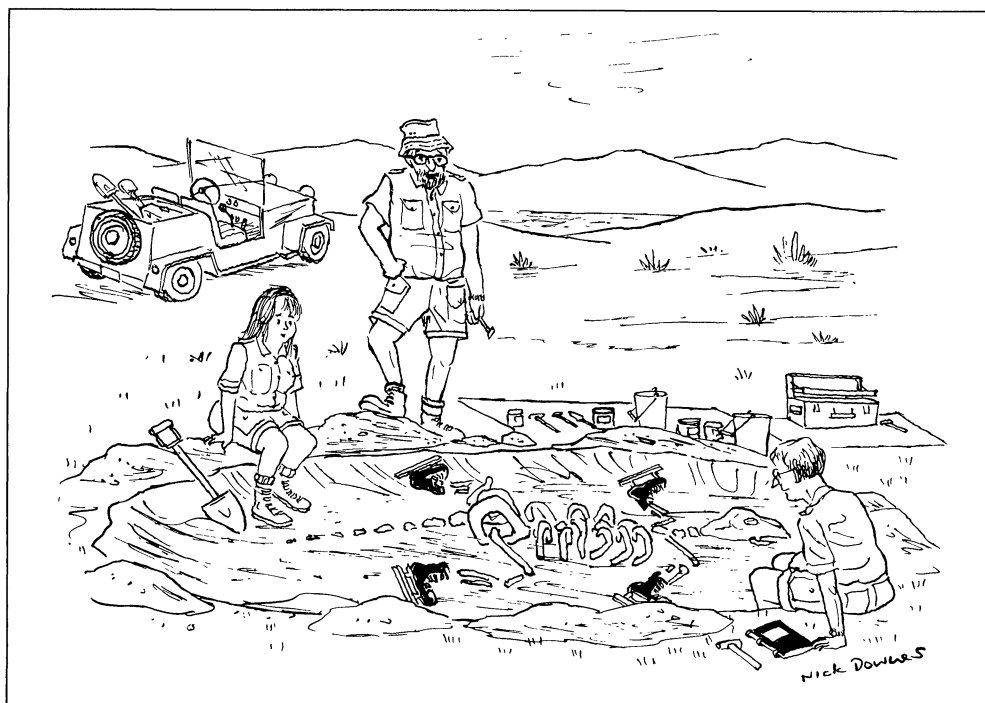
Fig. 3. Effect of chronic desipramine treatment on cocaine-induced cocaine craving. Intravenous cocaine (0.5 mg per kilogram of body weight) or cocaine placebo infused in five subjects after long-term treatment with desipramine hydrochloride (150 mg/day for greater than 10 days) or placebo maintenance. (□, placebo/placebo; ◆, placebo/desipramine; ■, cocaine/placebo; ◇, cocaine/desipramine)

ponents. Initial clinical investigations of how the "normal euphoria of a healthy person" (7) becomes transformed into the source of "mad craving" (6) have resulted in the promise and initial actualization of advances in pharmacological and psychotherapeutic treatment of cocaine addiction. These advances have been founded in basic animal research, thus underscoring the value of basic research directed at unraveling the neurophysiological mysteries of human experiences of pleasure and pain.

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"Whatever it was, it was around during the ice-age."