



REVIEW

Drug addiction: Pathways to the disease and pathophysiological perspectives[☆]

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Received 16 May 2006; received in revised form 28 August 2006; accepted 24 October 2006

KEYWORDS

Drug addiction;
Definition
physiopathology

Abstract Drug addiction is a medical condition, a chronic relapsing disease. As in other domains of experimental medicine, appropriate experimental investigations are needed in order to better understand the disease. However, to understand the diverse facets of drug effects and of the underlying pathophysiology it is necessary to keep in mind the complexity of the psychopathological processes. The main symptoms that characterize addiction correspond to expressions of dysfunctions within specific circuits and regions. Pathways to addiction are numerous and comorbidity and in the real world poly-drug use are common. Some of these aspects will be examined as well as the role of life events and stress. Theoretical considerations will be proposed [see also: Koob, G.F., & Le Moal, M.. 2005a. *Neurobiology of Addiction*. Elsevier. 570 pp] to account for the stages of the disease from impulse control disorder to compulsive disorders, for affective dynamics and for the relations between the symptoms and pathophysiology.

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1. The problem of definition

Historically, the last stages of a drug misuse escalation was defined as a state of dependence, “an arbitrary term used to denote the presence of an acquired abnormal state wherein the regular administration of adequate amount of a drug has, through previous prolonged use, become requisite to physiologic equilibrium. Since it is not yet possible to diagnose physical dependence objectively without withhold-

ing drugs, the sine qua non of physical dependence remains the demonstration of a physical abstinence syndrome” (Himmelsbach, 1943). This authoritative definition evolved into the definition of physical dependence, an intense physical disturbance when drug usage was discontinued. Then, when no physical signs were observed, obvious other aspects of the process were considered, in particular the behavioral and psychic symptoms, resulting in the definition of psychic dependence, a condition in which a drug produces “a feeling of satisfaction and a psychic drive that require periodic or continuous administration of the drug to produce pleasure or to avoid discomfort...” (Eddy et al., 1965). More recent definitions resemble a combination of Himmelsbach's physical and psychic dependence with emphasis on the psychic and motivational aspects of withdrawal: “Addiction comes from the Latin verb “addicere”, to give or bind a

[☆] Michel Le Moal is the recipient of the 2005 ECNP Neuropsychopharmacology Award in Basic Science. This paper has been written to mark this occasion.

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person to one thing or another. Generally used in the drug field to refer to chronic, compulsive, or uncontrollable drug use, to the extent that a person (an “addict”) cannot or will not stop the use of some drugs. It usually implies a strong (Psychological) Dependence and (Physical) Dependence resulting in a Withdrawal syndrome when use of the drug is stopped. Many definitions place primary stress on psychological factors, such as a loss of self-control and overpowering desires, i.e., addiction is any state in which one craves the use of a drug and uses it frequently. Others use the term as synonym for physical dependence; still others see it as a combination (of the two)” (Nelson et al., 1982). Finally, the word dependence has multiple meanings. Any drug can produce dependence if dependence is defined as the manifestation of a withdrawal syndrome upon cessation of drug use, but meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) (American Psychiatric Association, 1994), in which criteria for substance dependence is much more than a manifestation of a withdrawal syndrome, but rather is equivalent to addiction. The word addiction, with its precise meaning (O’Brien et al., 2006), is now largely admitted.

Modern views have focused on three types of drug use: (1) occasional, controlled or social use, (2) drug abuse or harmful use, and (3) drug addiction. Clinically, the occasional but limited use of an abusable drug is distinct from escalated drug use, loss of control over limiting drug intake, and the emergence of chronic compulsive drug-seeking that characterizes addiction. Drug addiction, (substance dependence, American Psychiatric Association, 1994), is a chronic relapsing disease that is characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake (3) emergence of negative emotional states (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (Koob and Le Moal, 1997). An important goal of current neurobiological research on addiction is to understand the neuropharmacological and neuroadaptive mechanisms within specific neurocircuits that mediate the transition between occasional, controlled drug use and the loss or behavioral control over drug-seeking and drug-taking that defines chronic addiction (Koob and Le Moal, 1997). It is hypothesized that this transition corresponds to the passage from a normal state to an allostatic state and finally a pathological one, i.e., a chronic and relapsing disease. The critical nature of the distinction between harmful abuse and addiction is illuminated by epidemiological studies that show that a very limited percentage of the users will become dependent or addict. Recent data derived from the National Household Survey on Drug Abuse (Substance Abuse and Mental Health Services Administration, 2003) showed that the percentage addicted to a given drug, of those who ever used, decreases in the following order: heroin, cocaine, marijuana, alcohol, tobacco being, by far, the most addictive product. Fundamentally, a large scale of individual differences characterizes the passage to the disease: a few of those who use drugs would succumb, suggesting an individual intrinsic vulnerability, the causes of it, inherent or acquired, are at the core of the etiological investigations. However, it is important to bear in mind that some individuals may become addicted almost after a first encounter with a drug.

Addiction, as a chronic relapsing disease (Meyer, 1996) resembling asthma, diabetes, or hypertension, is defined by

its diagnosis, aetiology, and pathophysiology. The associated medical, social and occupational difficulties that develop during the course of addiction (Fig. 1) do not disappear after detoxification and the changes in brain due to addictive drugs endure long after the patient stops taking them and that explains the high risks of relapse, from 60 to 80% within the year following discharge, according to the class of drug (McLellan et al., 2000, 1996; O’Brien and McLellan, 1996). The neuroadaptive changes due to drug administration have been explored from molecular (Nestler, 2001) to system levels by means of preclinical models. Different aspects, according to different interests or theories, or to the stages of the process (vulnerability, transitions from drug use to dependence, stages of addiction) are considered. Psychopathological dimensions are linked to specific alterations in given structures or circuits. There is, first, an incentive-sensitization view (Robinson and Berridge, 1993; Robinson and Berridge, 2003) for which sensitization of neural systems, including dopamine neurons, that attributes incentive saliences causes compulsive motivation to take drug. Complementary to this view it is now admitted that changes in glutamatergic interconnections between the ventral tegmental area, nucleus accumbens, prefrontal cortex and amygdala contribute also to the neural changes (Nestler, 2001; Vanderschuren and Kalivas, 2000). A second view prioritizes reward related learnings, the development of strong stimulus-response habits, aberrant memories and maladaptive behaviors at the basis of the addiction process (Everitt and Robbins, 2005; Hyman et al., 2006; Kelley, 2004). There are reciprocal pathological feed-forward links between core motivational systems within basal brain regions (hypothalamus, brainstem) and higher order limbic and corticostriatal structures. In a neurocognitive perspective, a third view is concerned by the imbalance between two interacting functional-structural systems, one that controls decision making, i.e., an impulsive amygdala system

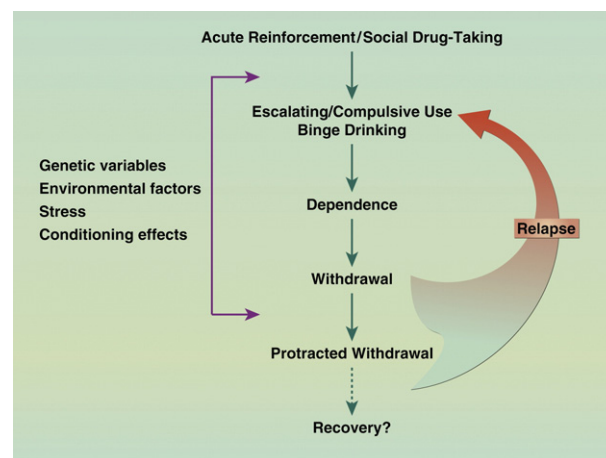


Figure 1 Stages of addiction to drug of abuse. Drug-taking begins with social drug-taking and acute reinforcement and sometimes, for some individuals, then moves in a pattern of escalating compulsive use and finally to dependence, withdrawal and protracted abstinence. Relapse is likely to occur and the cycle is repeated. Many factors, genetic, environmental contribute to the vulnerability to enter in the cycle. Reproduced with permission from Koob and Le Moal (2005a).

for signaling pleasure (and pain) for immediate prospects and a reflective prefrontal cortex system for signaling future prospects (Bechara, 2005). Complementarily to these bottom-up signals, there is a progressive transition from prefrontal cortical to striatal control over drug seeking as well as a progression from ventral to more dorsal domains of the striatum, i.e., from impulsive to compulsive drug use (Everitt and Robbins, 2005). A fourth view synthesizes aspects of the other theories and includes pathophysiological considerations such as hedonic allostasis and opponent processes (Koob and Le Moal, 2005a,b).

The diagnostic criteria for addiction have evolved over the last decades (O'Brien et al., 2006) with a shift from an emphasis on tolerance and withdrawal to criteria directed more at compulsive use (Substance Abuse and Mental Health Services Administration, 2003). The number of criteria met by drug addicts varies with the severity of the disease, the stage of the process, and the drug abused. For example, in adolescents, the most frequently observed criteria are much time getting or recovering from drug use (DSM IV, criteria #5 and #7), continued use despite problems in social and occupational functioning (criterion #6), and tolerance or withdrawal (criteria # 1 and # 2) (Crowley et al., 1998).

2. Perspectives and research interests

The field of addiction research is as large as many other psychiatric problems, with sociological, environmental and developmental aspects, life events, various comorbidities, genetics, and the proper toxic intrinsic properties of drugs of abuse. Investigators in these various fields of research are generally confronted with the large individual differences concerning the propensity to take drugs and the vulnerability to succumb to addiction. Pharmacological approaches, especially in animal studies, are more concerned by drug properties and toxicological actions, without considering individual characteristics. In brief, the different fields of addiction research can be divided in two large groups: the ones place the individual, the addict, at the center of research or interests, the others place drugs and their pharmacological and intrinsic properties, as well as the dynamics of use behavior at the center of their interest. Table 1 resumes the characteristics of these two contrasting research fields. These two perspectives have different implications. If clinical aspects are considered, for drug-centered approaches addiction is, in some ways, an iatrogenic disorder while, for an individual-centered position, it is a biobehavioral disorder concerning a phenotype vulnerable (predisposition, comorbidity, life events, genetics) to the effects of drugs of abuse. When research and therapeutics are considered, the first position is oriented to understanding the effects of drugs of abuse on brain systems and cells and to counteract these effects by pharmacological means, while the second position is oriented towards prevention and detection of vulnerable individuals and towards psychosocial treatments. These two different research interests and practices have their own logic and necessities and must be considered as complementary: each is necessary but not sufficient and has limitations especially if addiction is examined through its clinical definition. A translation from the real world to the laboratory must develop or discover new models of addiction that will present 1) individual differences and

vulnerable phenotypes, 2) a transition from use to misuse and dependence and finally, 3) the main symptoms of the disease.

Besides a drug-centered view of addiction as discussed above, three individual-centered perspectives can be considered.

The first perspective is a psychiatric view. Here drug addiction is conceptualized as a disorder that progresses from impulsivity to compulsivity. Impulse control disorders are characterized by an increasing sense of tension or arousal before committing an impulsive act, but gratification, pleasure or relief at the time of committing the act, and after there may or may not be regret, guilt or self-reproach. Conversely, in compulsive disorders, recurrent and persistent thoughts in the form of obsessions that cause anxiety and stress are present before committing the compulsive repetitive behavior and relief from stress appears by performing the compulsion. As a subject moves from impulse control disorders to compulsivity (Fig. 2), there is a shift from positive reinforcement for driving the motivated behavior to negative reinforcement driving the motivated behavior. The disease progresses in a spiraling/distress cycle comprising three stages: preoccupation/anticipation, binge/intoxication, withdrawal/negative affect (Koob and Le Moal, 1997). However the psychiatric view is by nature preoccupied by the "why" that makes some individuals prone to enter in the disease cycle.

A second perspective is the psychodynamic view with a focus on the factors leading to vulnerability for addiction. This perspective, illustrated by Khantzian's research (Khantzian, 1985, 1990, 1997), is rooted in clinical practice and in modern psychodynamic concepts in relation to substance use disorders. The focus of this approach is on developmental difficulties, emotional disturbances, structural (ego) factors, personality organization, and the building of the self. This contemporary perspective contrasts with a classic but not

Table 1 Research interests and questions for theories of addiction

I. Drug-centered research interests and questions

1. Pharmacological and intrinsic properties of drugs
 - mechanisms of action, from functional to molecular levels,
 - properties: are they general or specific for each drug?
2. Dynamics of use behavior
 - transition to dependence: a general phenomenon or specific characteristic for each drug?
 - addiction: is it a unitary process?

II. Individual-centered research interests and questions

1. Individual and differential vulnerabilities or resilience
 - importance of genetics and/or environmental factors,
 - characteristics of a vulnerable versus a resilient individual: are these characteristics general or particular for each subject.
2. Developmental and life space structures and dynamics
 - characteristics of developmental/environmental factors conducive to drug abuse; role of comorbidities,
 - can changes in environment and live conditions change drug abuse proneness?

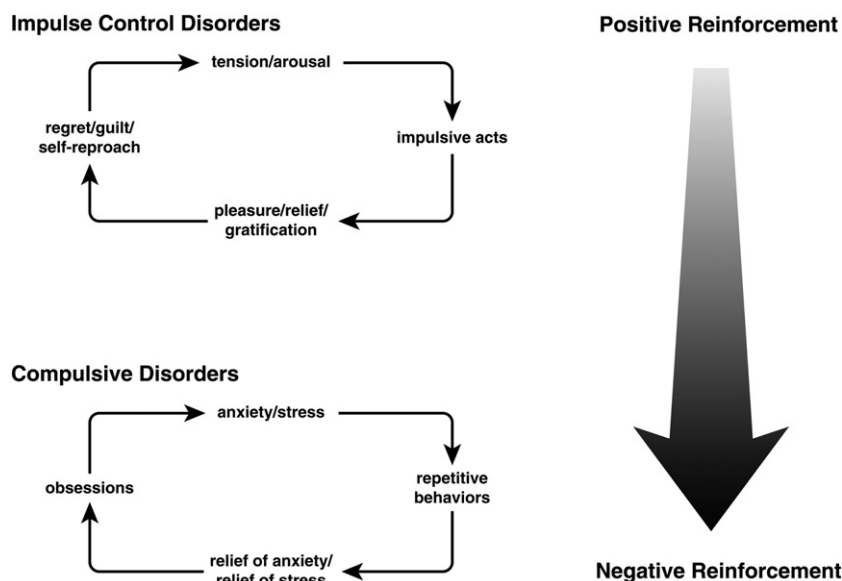


Figure 2 Stages of impulse control disorder and compulsive disorder cycles related to the source of reinforcement. In the first stage increasing tension and arousal occur before the impulsive act, with pleasure, gratification, or relief during the act; following the act there may or may not be regret or guilt. In compulsive stages, there are recurrent and persistent thoughts (obsessions) causing stress and anxiety followed by repetitive behaviors (compulsions) that are aimed at preventing or reducing distress (DMS IV). Positive reinforcement (pleasure/gratification) is more related to impulse control disorder while negative reinforcement (relief of anxiety or relief of stress) is more closely associated with compulsive disorders. Reproduced with permission from Koob (2004).

abundant psychoanalytic literature on the subject that emphasizes the pleasurable aspects of drugs and the regressive aspects of drug use. Two elements, disordered emotions and disordered self-care and self-preservation, and two contributory elements, disordered self-esteem and disordered relationships, have been identified to evolve into a modern self-medication hypothesis, where individuals are hypothesized to take drugs as a “means to cope with painful and threatening emotions”. Here, subjects experience states of subjective distress and suffering that may or may not be associated with conditions meeting DSM-IV criteria; they have feelings that are overwhelming and unbearable and may consist of an affective life that is absent and nameless. Others subjects suffering of alexithymia cannot express personal feelings and access to their emotions (Sifneos, 2000). Importantly, such self-medication, at least at the beginning of the process, may be drug-specific with a preferential use of a class of drugs that fit with the nature of a painful affective state or particular comorbidity. Opiates might be effective in reducing psychopathological states of violent anger and rageful feelings. The activating properties of psychostimulants will be preferred in case of anhedonia, anergia, or lack of feelings. Some subjects flooded in their feelings, or cut off from feelings, will welcome repeated moderate doses of alcohol or depressants as medicine to express feelings they were not able to communicate. In brief, each class of drugs serves as an antidote to dysphoric states and as a replacement for a defect in the psychological structure. The paradox is that the choice of drugs to self-medicate such emotional pain will progressively promote intoxication and addiction in reason of proper effects on the brain and perpetuate a distressful life now revolving around drugs. This approach integrates a critical role of dysregulated brain reward and stress systems.

A third perspective corresponds to a self-regulation view of addiction, derived from social psychology. It has been argued that self-regulation failures were at the root of the major social pathologies in present times; they may lead to addiction in the case of drug use or an addiction-like pattern with non-drug behaviors (Baumeister et al., 1994). There are important self-regulation elements involved in the different stages of addiction, as well as other pathological behaviors and biobehavioral disorders such as compulsive gambling, binge eating, violence and antisocial responses. Under-regulation as reflected in strength deficits, failure to establish standards or conflicts in standards, and attention failures as well as misregulation (misdirected attempts to self-regulate) can contribute to the development of addiction-like patterns of behavior. The transition to addiction can be facilitated by 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 leading to spiraling distress. In some cases, the first failure leads to emotional distress which sets up a cycle of repeated failures to self regulate and where each violation brings additional negative affects, resulting in spiraling distress (Baumeister et al., 1994). For example, a failure of strength may lead to initial drug use or relapse, and other self-regulation failures can be recruited to produce an entrance to, or prevent an exit from, the addiction cycle.

Such dysregulation is reflected in deficits in information-processing, attention, planning, reasoning, self-monitoring, inhibition, and self-regulation, many of which involve functioning of the frontal lobe (Giancola et al., 1996). Executive function deficits, self-regulation problems, and frontal lobe dysfunctions or pathologies constitute a risk factor for biobehavioral disorders (Dawes et al., 1997).

Deficits in frontal cortex regulation in children or young adolescents are good predictors for later drug and alcohol consumption, especially for children raised in families with drug and biobehavioral disorders histories (Aytaclar et al., 1999; Dawes et al., 1997).

These perspectives, and also the dependence view, have in common to consider pathways to addiction as leading to a dynamic spiral where a spiraling distress cycle increases in amplitude with repeated experience.

As discussed above, drug usage by itself is not, and far from it, the mechanical cause leading to the stage of addiction. Intrinsic individual elements will determine who will succumb or not. Misuse escalation, prolonged use, the drug by itself, in reason of its neurotoxic properties and the subsequent pathophysiological changes is the agent acting on a vulnerable back-ground. A state of vulnerability is neurobiologically implemented and this state interacts with the pharmacological processes. To consider the cause of vulnerability means to hark back to the perspectives of individual-centered views of addiction.

Finally, drug abusers represent a highly heterogeneous group. As seen above, as individuals meet or seek drugs of abuse, many of them are in a state of acquired or inherent vulnerability or pathologies with their correlative brain deregulations (Baumeister et al., 1994; Dawes et al., 1997; Giancola et al., 1996; Khantzian, 1997). The patterns leading to dependence are diverse (de Wit et al., 1986; O'Brien et al., 1987). Individual differences in temperament, social development, comorbidity, protective factors, and of course genetics are area of intense research. A reasonable assertion is that the initiation of drug abuse is more associated with environmental and social factors, whereas the movement to abuse and addiction is more associated with neuropharmacological and neurobiological factors (Glantz and Pickens, 1992). Developmental factors are important components of vulnerability. Adolescent exposure to licit or illicit drugs leads to significant vulnerability for drug problems, alcohol in particular, in adulthood. Subjects first intoxicated at 16 or younger were more likely to drive after drinking, to ride with intoxicated drivers, to be injured seriously when drinking, to be more likely to become heavy drinkers, and to be more likely to develop alcohol dependence (Hingson et al., 2003). Nowadays, smoking initiation occurs at 14-15 years of age. The age at which smoking begins influence the total years of smoking, the number of cigarettes smoked in adulthood, and the likelihood of quitting (Chassin et al., 1990). When prevalence of lifetime illicit or non-medical drug abuse and substance dependence was estimated for each year of onset of drug use from ages 13 and younger to 21 and older, early onset of drug use was a significant predictor of the subsequent development of drug abuse over a lifetime: overall the prevalence among those who started under the age of 14 was 34% but 14% for those who started using at 21 or older (Grant and Dawson, 1998). There is a considerable support for the hypothesis that initiation begins with legal drugs and involvement with illicit drugs later in the developmental sequence, marijuana being a bridge in the path to more addictive drugs (Kandel and Jessor, 2002). Poly-drug uses concern the majority of addicts. Although common, the sequence is not inevitable and concerns a limited percentage of youths. Other factors of vulnerability concern temperament and comorbidity. Temperament clusters and personal-

ity traits include inhibition and control failures, negative affects, novelty and sensation-seeking, temperament (Glantz, 1999). The strongest associations with comorbid psychiatric disorders are found with mood and anxiety disorders, antisocial personalities and conduct disorders (Glantz and Pickens, 1992). Large epidemiological studies (30000 subjects) have revealed that approximately 35% of addicts met lifetime criteria for a mood disorder, 45% for an anxiety disorder, and 50% for either conduct or antisocial personality disorder (Merikangas et al., 1998). More recent investigations (43000 subjects) confirm these data: 21-29% for comorbidity of mood disorders, 22-25% for anxiety disorders, 32-70% for personality disorders (Grant et al., 2004a,b). Genetic contributions to addiction have long been postulated and can result from complex genetic differences that range from alleles that control drug metabolism to hypothesized genetic control over drug sensitivity and environmental influences. Complex influences are those that are not genetic but are not due to single-gene effects that produce Mendelian inherent patterns (Uhl and Grow, 2004). The classical approaches to complex trait genetics have been the examination of comorbidity for the trait in monozygotic versus dizygotic twins, reared together or apart, and in analogous family studies with other sorts of biological relatives. Estimates of the extent of genetic effects - heritability - have computed that genetic factors can account for approximately 40% of the total variability of the phenotype, which argues for gene-environment interactions, including the stages of the addiction cycle, developmental and social factors. Interestingly, it is suggested that there is a significant overlap between genetic predisposition for dependence on most classes of addictive substances (Karkowski et al., 2000). It remains to be known as to which factor of vulnerability, specific or not, genetic factors account. It is important to note that genetic and environmental-social factors can convey protection and resilience against drug abuse.

3. Stress and addiction: from environment to pathophysiology

The role of stressors and the process of stress provide a good example for understanding the genesis of a vulnerable condition and, as the process is going on, the passage to addiction and its related pathophysiology. The brain and brain pituitary stress system have a role in the initial vulnerability to drugs of abuse and in the vulnerability to relapse (Goeders, 1997; Kreek and Koob, 1998; Piazza et al., 1996; Piazza and Le Moal, 1997, 1998). Laboratory studies have abundantly demonstrated the deleterious effects of stress and it is generally admitted that stressors, life events, social pressure and breakdown, prenatal stress, all factors that induce allostatic states and individual differences are factors of vulnerability and relapse. Stressors facilitate the acquisition of drugs of abuse self-administration, and food restriction increases self-administration of drugs and these effects are related to glucocorticoid release. Stress, through activation of the hypothalamic-pituitary-adrenal axis and the release of glucocorticoids influences many regions of the brain, including dopamine neurons, that express corticoid receptors (Harfstrand et al., 1986). In normal situations, glucocorticoids state-dependently increase dopaminergic

functions, especially in mesolimbic regions, during various consummatory behaviors exhibited in the rodents active period of the light/dark cycle and also in animals shown to self-administer drugs. The interaction of glucocorticoids with the mesocorticolimbic dopamine system may have a significant impact on vulnerability to self-administer drugs of abuse. In basal condition, glucocorticoid secretion and dopamine release are low, as the result of sensitivity to drug of abuse. An acute stress causes an increase in glucocorticoid secretion, which, by enhancing the release of dopamine, results in an increase in the sensitivity to the reinforcing effects of drugs of abuse, and thus in an increase in self-administration. The repeated exposure to stress and a consequent repeated increase in the concentration of glucocorticoids progressively impair glucocorticoid negative feedback by decreasing the number of central corticoid receptors in the hippocampus. This produces a long-lasting increase in the secretion of glucocorticoids and an increase in the release of dopamine in the nucleus accumbens and that explains why, after repeated stress, an increase in the sensitivity to drugs is found also weeks after the end of the stressor exposure. Stress reactivity is a reliable predictor for vulnerability to abuse. Naïve rats selected for an initial high reactivity in a mild stressful novel environment present a higher reactivity of the stress axis and are more likely to self-administer drugs (Piazza and Le Moal, 1996, 1997; Piazza et al., 1996). Moreover, rats receiving repeated injections of corticosterone acquire cocaine self-administration at a lower dose than do rats that self-administer vehicle; in addition, rats that normally do not self-administer drugs, i.e., that do not react to the novel environment, have a lower stress axis reactivity but become prone to get drugs after stress or corticosterone administration (Piazza et al., 1991a,b). Conversely, surgical adrenalectomy and blockade of glucocorticoid receptors (and also CRF receptors) tend to suppress drug self-administration in rats (Goeders, 1997, 2002; Piazza and Le Moal, 1996). Glucocorticoid hormones and stimulants interact at the same cellular levels, particularly the shell region of the nucleus accumbens (Barrot et al., 2000) and animals, especially those that react more to stress and to stimulants, self-administer glucocorticoids in the same way as they do for psychostimulants (Piazza et al., 1993). These results suggest that stress hormones may be one of the biological factors determining vulnerability to substance use and that it is possible to predict proneness to drug use: the most reactive rats to stressful situation, or those with the most reactive stress axis will be, occasionally, those that will take drugs. There is a pathophysiological process, from stress to increased dopamine utilization, to increased sensitivity to drugs (Piazza et al., 1993, 1996; Piazza and Le Moal, 1997) that can be acquired by some individuals. As an example of acquired dysfunctions after environmental events, prenatal stress increases and prolongs in offspring (when adult) corticosterone secretion in response to stress, increases behavioral reactivity to stress and increases drug self-administration (Deminière et al., 1992). The differential vulnerability is demonstrated after dose-response, dose-intake, and ratio-intake studies; large variations in cocaine-reinforcing efficacy exist, producing dramatic differences among animals for drug intake across doses; these vulnerable subjects would have a higher chance of developing addiction independent of the quantity of drug

available, as it occurs in the real world (Piazza et al., 2000). Moreover, differential sensitivity to the drug and to self-administration correlates with reduced dopamine activity in the prefrontal cortex and increased dopamine utilization in the nucleus accumbens (Piazza et al., 1991a,b). Conversely, drugs of abuse stimulate hypothalamic-pituitary-adrenal axis by acting on CRF transmission (Rivier and Vale, 1987).

Acute stress or histories of harmful life events undoubtedly have a role both in the initial vulnerability to drugs and in relapse; however, as dependence develops drugs ultimately engage brain stress CRF systems and noradrenaline stress systems (Koob, 1999; Koob, 2003). Acute withdrawal from all the drugs of abuse produces increases in CRF release as measured by *in vivo* microdialysis in the central nucleus of the amygdala and in some cases in the bed nucleus of the stria terminalis (BNST); moreover, CRF antagonists block the increased anxiety or aversive responses associated with precipitated drug withdrawal (for review: Koob and Le Moal, 2005a) and more specifically, a competitive CRF1 antagonist block the development of place aversion to precipitated opiate withdrawal (Stinus et al., 2005). These increases in CRF have motivational significance in that competitive CRF antagonists block the increased drinking in dependent rats but not baseline non-dependence drinking (Valdez et al., 2002). Recently it has been shown, by using mice lacking dopamine beta-hydroxylase, an enzyme critical for noradrenaline synthesis, that this amine was necessary for morphine-induced conditioned place preference and locomotion and that these deficits were rescued by systemic noradrenaline restoration (Olson et al., 2006). Moreover these authors evidenced that viral restoration of the enzyme in the nucleus tractus solitarius, but not in the locus coeruleus, restored selectively place preference for morphine, in other words that the noradrenergic transmission from the nucleus tractus solitarius was necessary for opiate reward. Noradrenergic projections to the BNST, issued from the caudal medulla through the ventral bundle activate CRF systems and are critically involved in the motivational aspects of opiate withdrawal (Aston-Jones et al., 1999; Aston-Jones and Harris, 2004; Delfs et al., 2000; Markou and Koob, 1991) and microinjections of beta-adrenergic receptor antagonists or of an alpha 2-receptor agonist into the BNST block opiate withdrawal-induced conditioned place aversion, as does a lesion of the ventral bundle. Immunohistochemical studies revealed that numerous BNST-projecting cells in the A₁ and A₂ noradrenergic cell groups of the caudal medulla were activated during withdrawal (Delfs et al., 2000); moreover lesion studies showed that locus coeruleus noradrenergic projections had no effect. These data suggest that these two brain stress systems may be activated during the development of addiction and contribute to the motivation for excessive drug seeking associated with dependence (Koob and Le Moal, 2004). Neuropeptide Y, an anti-stress neural system, is dysregulated as a “brake” on the stress systems, increasing their dysregulation (Heilig et al., 1994). These dysregulations persist during protracted abstinence and can be reinstated by an acute stressor. In rats dependent on alcohol and tested 2-6 weeks post-acute withdrawal, intracerebroventricular administration of a competitive CRF antagonist blocks an enhanced anxiety-like response in an elevated plus-maze (Valdez et al., 2003) and parallel results obtained with chronic morphine treatment have also shown increases in Fos staining

in the cingulate cortex, basolateral amygdala, and ventral part of the BNST (Harris and Aston-Jones, 2003). Again, release of noradrenaline in response to stressors elevates anxiety that then augments the reward value of drugs through negative reinforcement (Koob and Le Moal, 2004). Stress-induced reinstatement long after abstinence in humans and animals is well documented; it is not blocked by removal of the glucocorticoids but by CRF1 receptor antagonists with a suggested site of action in the ventral BNST, and a CRF-containing pathway from the central amygdala to BNST (Erb et al., 2000; Erb and Stewart, 1999; Shaham et al., 1998, 1997). Noradrenergic functional antagonists infused into the BNST block stress-induced reinstatement, as does a lesion of the ventral noradrenergic bundle (Erb et al., 2000; Leri et al., 2002; Shaham et al., 2000). The exact interaction between the noradrenergic projections and the intrinsic CRF systems of amygdala and BNST are not known but may involve activation of CRF by the noradrenergic pathway to the BNST region, which in turn may activate noradrenergic systems in the ventral medulla (Koob, 1999; Shalev et al., 2002). Such a feed-forward system has been hypothesized for CRF/noradrenergic interactions for anxiety and stress-like responses and may become activated during the development of addiction.

4. Neuroadaptational perspectives

4.1. Counteradaptational-opponent process

Counteradaptation hypotheses have long been proposed to explain tolerance and withdrawal and the motivational changes associated with the transition to addiction. Clinical observations and animal experiments show that the initial acute effect, in some ways the unconditional effect, of the drug is opposed or counteracted by homeostatic forces in systems, in some ways a conditional effect, that mediate primary drug actions (Hoffman and Solomon, 1974; Martin, 1968; Poulos and Cappell, 1991; Siegel, 1975). This view reminds earlier works cited above on physical dependence (Himmelsbach, 1943) and the counteradaptive changes associated with acute and chronic opioid administration on physiological measures.

Predated by the views of Martin (Martin, 1968; Martin and Eades, 1960), Opponent-Process Theory was developed during the 1970s by Solomon and colleagues (D'Amato, 1974; Hoffman and Solomon, 1974; Solomon and Corbit, 1973), on the basis of various physiological, behavioral and pharmacological observations. It has been applied by many authors to various situations such as drugs (opiates, nicotine, alcohol) to adjunctive drinking, fear conditioning, tonic immobility, ulcer formation, eating disorders, tonic immobility, ulcer formation, eating disorders, jogging, peer separation, glucose preference and parachuting (for review: Solomon, 1980). The theory assumes that the brain contains many affect control mechanisms, working as though they were affect immunization systems that counter or oppose all departure of affects, pleasant or aversive, from equilibrium. The device is composed of subparts organized in a temporal and dynamic manner: two opposing processes and a summator, which determines the controlling affect at a given moment. In time, first, an unconditional arousing stimulus triggers a primary affective process: the a-process; it is an unconditional reaction that translates the intensity, quality, duration of the stimulus, for example the

first opiate intake. Then, second, as a consequence of the a-process, inherently linked to it on a biological basis, the b-process is triggered after a short delay as an opponent process. Empirically, the b-process feeds an opponent signal into the summator that substrates its value to the already ongoing a-process. The apparent response is, dynamically, the algebraic sum of the two processes. The two processes are temporally, consequently linked, "a" the unconditional response triggering "b", conditional, but they are hypothesized to depend on different, while linked, neurobiological mechanisms. The b-process has a longer latency, but some data show that it may appear soon after the beginning of the stimulus and in the course of the stimulus action (Larcher et al., 1998), and it has a more sluggish decay (Fig. 3).

From a drug addiction perspective, the theory posits that tolerance – in terms of drug efficacy it is an apparent tolerance – and dependence are inextricably linked. The first few self-administrations of an opiate drug produce a pattern of motivational changes where the onset of the drug effect produces a euphoria – the a-process followed by a decline in intensity; then, after the effects of the drug wear off, the b-process emerges as an aversive craving state. The b-process gets larger and larger over time, producing more apparent tolerance to the initial euphoric effects of the drug. The dynamics, with the repetition of the stimulus, is the result of a progressive increase in the b-process: in other words the b-process sensitizes through drug use, appears more and more rapidly after the unconditional stimulus onset, lasts longer and longer (the conditional effect) and masks the unconditional effect (a-process), resulting in an apparent tolerance. As said before, the two processes, while interdependent, activate specific cellular systems and the final drug response results of dynamics between systems (Koob and Bloom, 1988).

As an example relevant to clinical observations, animal studies have documented the appearance of a hyperalgesia during spontaneous or precipitated opioid withdrawal (Célérier et al., 2001; Larcher et al., 1998; Laulin et al., 1999). In brief, opioid administration in rats induces as expected analgesia first, (unconditioned response) and hyperalgesia (conditioned response) is hypothesized to be an actual sensitization of pain facilitatory systems because both magnitude and duration of the hyperalgesia increase as a function of opioid administration, i.e., a first heroin administration in rats induces a moderate hyperalgesia for 2 days, whereas the fifth injection of the same dose is followed by hyperalgesia for 6 days (Célérier et al., 2001). When the opioid is administered repeatedly (once daily for two weeks), a gradual and dose-dependent lowering of the nociceptive threshold is observed (Fig. 4), lasting several weeks after drug administration (Célérier et al., 2001). A small dose of heroin, which is ineffective at triggering a delayed hyperalgesia in non-heroin-treated rats, induced an enhancement in pain sensitivity for several days after a series of heroin administrations, suggesting a sensitization phenomenon (Célérier et al., 2001). The effectiveness of the opioid receptor antagonist naloxone in precipitating hyperalgesia in rats that had recovered their pre-drug nociceptive value after single or repeated heroin administrations indicates that heroin-deprived rats were in a new biological state associated with a functional balance between opioid-dependent analgesic systems and pro-nociceptive systems. It is now well documented that the sensitization phenomenon (b-process) involves glutamate transmissions and it has been shown that the noncompetitive glutamate receptor

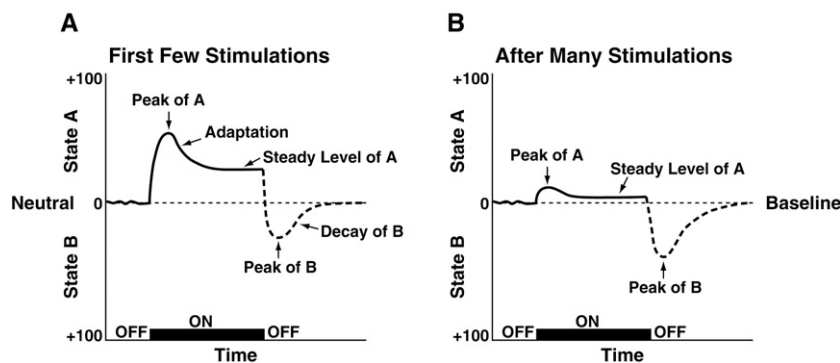


Figure 3 (A) The standard pattern of affective dynamics produced by a relatively novel unconditioned stimulus inducing first an unconditioned response, here A, and then, in consequence, a conditioned opposite response, here B; (B) The pattern of dynamics produced by a repeated stimulus resulting in an increased, sensitized conditioned B response that invades the unconditional A response. Reproduced with permission from Solomon (1980).

antagonist MK-801 prevented both heroin-induced long-lasting enhancement in pain and naloxone-precipitated hyperalgesia (Mao, 1999; Mao et al., 1994, 2002). As shown in Fig. 4, the receptor antagonist blocks the delayed effects of heroin, in other words the sensitized withdrawal effect manifested as hyperalgesia, or the lowering of the nociceptive threshold (b-process) which, with the passage of time, masks a sustained heroin analgesic functional effect. Again, this effect has led in past to an erroneous conclusion of an absolute decrease in the effectiveness of the drug: if the development of the b-process is blocked, no tolerance appears, the unconditioned effect of the drug does not change with repeated drug administration. The development of the b-process equals the development of a negative affective state and withdrawal symptoms, in opposition to the hedonic quality of the unconditional stimulus. The nature of the acquired motivation is specified by the nature of the b-process, that is, an aversive affect in the case of drug abuse. The subject will work to reduce, terminate, or prevent the negative affect. It is hypothesized that the behavioral and physiological observations cited above are the mirror of the underlying long-lasting pathological processes of addiction.

However more has to be done to decide between different interpretations of the sensitization process, for instance as a post-drug contemporary effect or as a delayed and non contingent drug effect. There is no doubt that previous experiences of drug, stress, etc... and that interferences between these experiences produce an increase of drug-induced behavioral measures in place preference conditioning, locomotor, stereotypic, taste conditioning, self-administration paradigms (Contarino et al., 1997; Covington and Miczek, 2001; Gaiardi et al., 1991; Lett, 1989; Shippenberg et al., 1996). Most of the studies show that there is no tolerance for the reinforcing properties of the drug per se. The long term consequences of the progressive neuroadaptive process may be reflected in a sensitization of the rewarding effects or in negative reinforcing effects of drug withdrawal, a negative affective state (Shippenberg et al., 1996). We have prioritized the concept of vulnerability, more central, the concept of sensitization being more connoted to motor sensitization. In human the hedonic response to one drug self-administration follows the above described a- and b-processes (see below, Fig. 5).

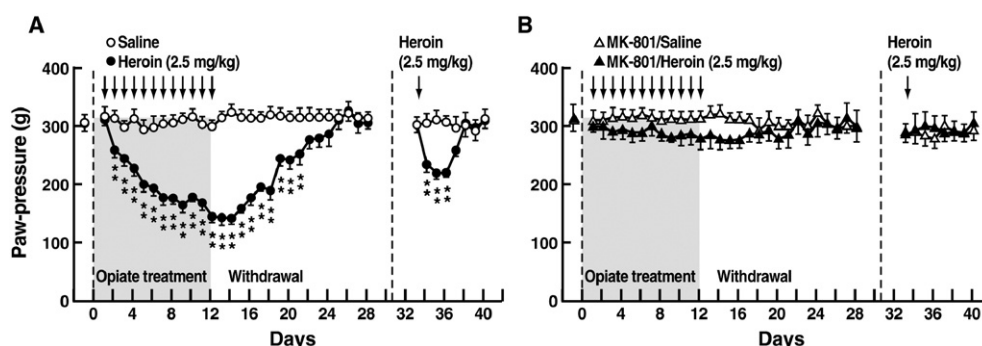


Figure 4 (A) Delayed effects of 12 once-daily heroin (2.5 mg/kg s.c.) or saline administration on basal nociceptive threshold in rats (black arrow). The basal nociceptive was determined daily before each heroin or saline administration and after the heroin was stopped. A very small dose (0.2 mg/kg) of heroin on day 33 when animals had recovered produces a large effect as if the pain system had been sensitized and in an allostatic state. Mean pressure for triggering vocalization (+/-SEM) was expressed in grams. ** $p < 0,01$ with Dunnett's test as compared to basal nociceptive value on Day 1. (B) Results obtained in experiment similar to A in rats receiving 12 coadministrations of the noncompetitive glutamate receptor antagonist MK-801 (0.15 mg/kg. s.c.) and heroin, or saline. The antagonist was administered 30 min before each heroin administration. Reproduced with permission from Célérier et al. (2001).

4.2. Motivational perspective

Emergence of a negative emotional state (dysphoria, anxiety, irritability) when access to the drug is prevented, i.e., dependence, (Koob and Le Moal, 2001) has been associated with this transition from drug use to addiction. Such a negative affective state can define dependence as it relates to addiction: “The notion of dependence on a drug, object, role, activity or 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....” (Russell, 1976). Rapid acute tolerance and opponent process-like effects to the hedonic effects of cocaine have been reported in human studies of smoked coca paste (Van Dyke and Byck, 1982). After a single smoking session, the onset and intensity of the “high” are very rapid via the smoked route of administration, and a rapid tolerance is manifest in that the “high” decreases rapidly despite significant blood levels of cocaine and subsequently, still despite significant blood levels of cocaine, human subjects report “dysphoria” (Fig. 5). The same phenomenon has been observed in rats: heroin was effective at inducing pain facilitation after only one exposure (Laulin et al., 1998). The analgesic action of one injection of heroin (2.5 mg/kg, s.c.) lasts for approximately 2 h (vocalization threshold to paw pressure) and declines to the predrug threshold in 4 h; afterwards, a significant lowering of nociceptive threshold appears. Interestingly allodynia was still observed 1-3 days after the injection, suggesting that it was an early sign reflecting neural plasticity associated with the development of dependence (Laulin et al., 1998), but the same neuroplasticity also may be involved in tolerance. In another human laboratory study, the “rush”, “high”, “low” and craving were averaged after an infusion of cocaine (0.6 mg/kg over 30 s). Both peak “rush” and “high” occurred 3 min post-infusion; peak “low”, with reports of dysphoria and paranoia occurred 11 min post-infusion; peak craving occurred after 12 min post-infusion (Breiter et al., 1997). Repeated or prolonged use of drugs is accompanied by a chronic perturbation in brain reward homeostasis. Brain changes moves to pathological neuronal maladaptations as moderate or short access drug use escalates to long access and compulsive use (Ahmed and Koob, 1998). The differential exposure to cocaine self-administration has dramatic effects on intracranial (medial forebrain bundle) self-stimulation (ICSS) reward threshold (Kenny et al., 2003; Markou and Koob, 1991). Such elevations in reward threshold begin rapidly and are observed within a single session of self-administration, bearing a striking resemblance to human subjective reports (Fig. 6). The animals self-administer more when the sessions are longer and the elevation in brain reward threshold following prolonged access to cocaine fails to return to basal levels between repeated, prolonged self-administration (i.e., residual hysteresis), thus creating greater and greater elevation (sensitization) in “baseline” ICSS threshold.

Here again even the unconditional response, i.e., the decrease of the threshold that follows immediately cocaine self-injections disappears, a phenomenon characteristic of an opponent process. These data evidence brain reward dysfunc-

tions in escalated cocaine self-administration that provide strong support for a hedonic allostasis model of drug addiction.

4.3. Allostasis and neuroadaptation

More recently, opponent process theory has been expanded into the domain of the neurocircuitry and neurobiology of drug addiction from a physiological perspective. An allostatic model has been proposed to explain the persistent changes in motivation and regulatory-control abilities that are associated with vulnerability to relapse, and this model has been generalized to the large group of psychopathologies associated with dysregulated motivational and control systems. Allostasis from the addiction perspective has been defined as the process of maintaining apparent functional stability through changes in brain reward and control mechanisms (Koob and Le Moal, 2001). The allostatic state represents a chronic deviation of reward and self-regulation set points that often are not overtly observed while the subject is actively taking the drug; it represents an acquired deviation from normal (homeostatic) functioning and abilities of the individual. Differences between homeostasis and allostasis are summarized in Table 2. Homeostatic regulation is on principle local in a defined system (intra-system) for a selective functional equilibrium, at the cellular level. Allostasis begins when a new equilibrium is needed and then other systems are recruited: it is inter-systemic, as is the b-process. Thus, the allostatic view is that not only does the b-process get larger with repeated drug taking, but the set points from which the a-process is anchored gradually shift downward (Fig. 7) creating an allostatic state (Koob and Le Moal, 2001). The allostatic state as compulsive drug taking and loss of control over drug taking is fueled by dysregulation of several neurochemical elements of reward circuits per se.

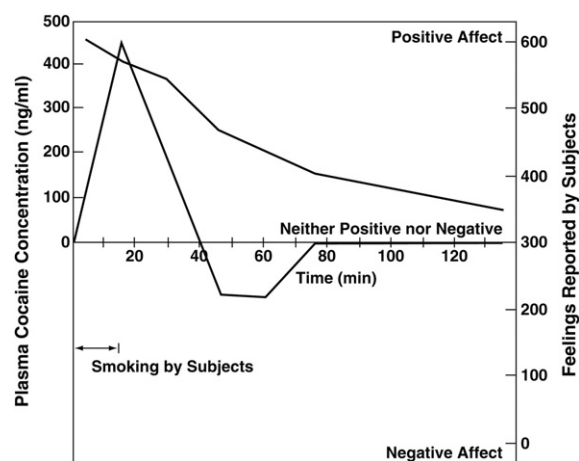


Figure 5 Dysphoric feelings (anxiety, depression, fatigue, desire for more drug) follow the initial euphoria in experimental subjects who smoked cocaine paste, even though the concentration in the blood remained relatively high. The peak feelings for the subjects were reached shortly before the peak plasma concentration, but the first psychological measurements were made later than the plasma assay. Dysphoric feelings oppose the euphoria, considered as the unconditional response to the drug. Reproduced with permission from Van Dyke and Byck (1982).

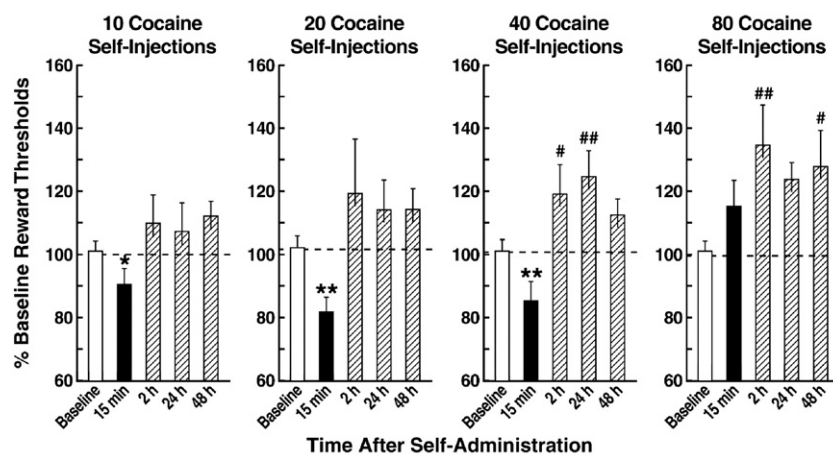


Figure 6 Rats were allowed to self administer 10, 20, 40, and 80 injections of cocaine (0,25 mg/inj.), and intracranial self-stimulation (ICSS) thresholds were measured 15 min and 2, 24, and 48 h after the end of each intravenous cocaine self-administration session. Horizontal dotted lines: 100% of baseline levels; data are means \pm SEM percentage of baseline ICSS thresholds. * $p < 0.05$, ** $p < 0.01$ compared to baseline; paired t -test; # $p < 0.05$, ## $p < 0.01$ compared to baseline; Fisher's LSD test after a statistically significant effect in the repeated measures analysis of variance. Reproduced with permission from Kenny et al. (2003).

It includes the central division of the extended amygdala (a basal forebrain macrostructure comprised of the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and a transitional area in the region of the shell of the nucleus accumbens). At the transmitter levels there is a decrease in the function of GABA, serotonin, dopamine, opioid peptides, an activation of hormonal responses of the HPA axis, mainly for the impulse control failure phase (positive reinforcement) and of the stress CRF and NPY brain systems, mainly for the compulsive disorder phase (negative reinforcement) (Fig. 8). There is also a dysregulation of prefrontal cortex-striatal loops. From data generated to date, it appears that the allostatic state and its constitutive structural elements (inter-systemic) are, at least in part, common to all addictions. These structural elements are now shared by most current neurobiological theories. Three components contribute to compulsive drug-seeking in addiction. A key element is due to compromised executive functions mediated by basal hypoactivity and situational hyperactivity in the orbitofrontal system; the functional consequences are a decrease of inhibition abilities, an increase in perseveration and impaired judgements. These changes in this key element impact on, or combine with, neuroplasticity in both enhanced conditioned reward mediated via the ventral-striatal-pallidal-thalamic cortical system with reward-stimulus associations increases and also impact on, or combine with, a compromised primary reward system mediated via the extended amygdala system with decrease of positive rewards and increase of anti-reward processes. Controversies exist, however, over the importance of the phenomenon of psychomotor sensitization associated with the mesolimbic dopamine system. According to the psychomotor sensitization framework, the wanting and liking of drugs are separate phenomena with separate neurobiological substrates, and a shift in an incentive-salience state described as wanting was hypothesized to be progressively increased by repeated exposure to drugs of abuse. The proponents of the sensitization theory have provided a substantial amount of data showing that imposed psychostimulant pretreatments cause a long-lasting augmentation of the effect of stimulants on striatal

dopamine activity (Kalivas and Duffy, 1988, 1993; Kolta et al., 1985; Parsons and Justice, 1993; Pierce and Kalivas, 1995, 1997; Robinson et al., 1985, 1982, 1988; Robinson and Berridge, 1993; Wolf et al., 1993). For the allostatic-neuroadaptational position locomotor activation or sensitization may play a role in initial sensitivity to a drug, but it disappears or becomes irrelevant with the development of motivational dependence.

The reinforcing effect of stimulant drugs is associated with elevated dopamine levels in ventral striatum. However in human subjects the stage of addiction involves other effects such as craving, loss of control, compulsive drug intake. By using positron emission tomography cocaine addicts and normal controls have been compared after intravenous methylphenidate (that causes an increase in synaptic dopamine like cocaine). Addicts showed reduced dopamine release in ventral striatum and also had a reduced "high" relative to controls. Interestingly addicts showed an increased response to the drug in the thalamus that was associated with craving; these effects were not seen in controls (Volkow et al., 1997). When cocaine addicted subjects are tested when watching a

Table 2 Homeostasis versus allostasis

Homeostasis	Allostasis
<ul style="list-style-type: none"> Equilibrium at a local level for a precise role 	<ul style="list-style-type: none"> New equilibrium by recruitment of several physiological systems
<ul style="list-style-type: none"> A set point at a normal level Set-point remains constant; no adjustment based on history 	<ul style="list-style-type: none"> Changing set-points Set-points adjustment and change based on history
<ul style="list-style-type: none"> Physiological equilibrium No anticipation of demand Adjustment carries no price 	<ul style="list-style-type: none"> Compensated equilibrium Anticipation of demand Adjustment and accommodation carry a price
<ul style="list-style-type: none"> No pathology 	<ul style="list-style-type: none"> Leads so pathology

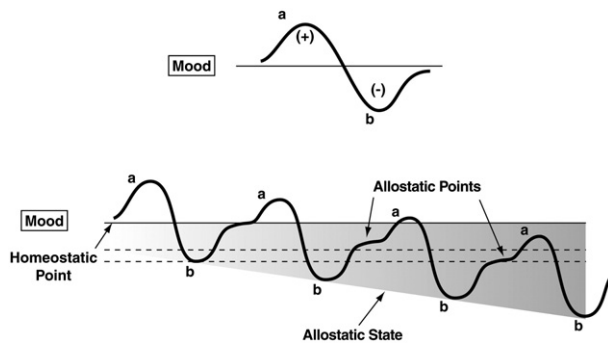


Figure 7 Diagram illustrating an extension of Solomon and Corbit's (1974) opponent-process model of motivation to outline the conceptual framework of the allostatic hypothesis accounting for the affective response to the drug. (Top) The diagram represents the initial experience of a drug with no prior drug history: the "a" process, the unconditional response, here a positive mood state, the "b" process is the unconditional, counteradaptive negative opposite response, here a negative mood state. The affective state is the sum of the successive processes but if drug use is not frequent or separated by sufficient intervals homeostasis remains and "a" process is mainly retained. (Bottom) With frequent repeated use the affective state moves to "b" process, out of homeostasis, but to allostasis and transition to addiction. A negative affective state is still present when an additional intake takes place. The counteradaptive opponent "b" process does not balance the activational "a" process but in fact shows a residual hysteresis. After a long period of abuse, and even during detoxification and a period of protracted abstinence the reward system is still bearing allostatic changes, a biological vulnerability. Reproduced with permission from Koob and Le Moal (2001).

neutral video versus cocaine-cue video (Volkow et al., 2006), specific binding of [^{11}C] raclopride was reduced in dorsal, but not in ventral striatum, and this reduction was correlated with self-report of craving. However, subjects with the highest scores on measures of withdrawal symptoms and of addiction severity had the largest dopamine changes in dorsal striatum, a region implicated in habit learning and in action initiation. The psychomotor sensitization hypothesis has been developed from imposed administration in laboratory animals. In normal human volunteers, repeated *d*-amphetamine provokes, after drug administration challenge an increase of activity-energy level, mood, amount of speech and eye-blink rates (Sax and Strakowski, 2001; Strakowski et al., 1996) but these data have been challenged especially when subject variability and group expectations are considered (Wachtel and de Wit, 1999). It is a classic clinical observation that individual differences exist for a vulnerability to develop paranoid psychotic state after long term stimulant use (Bartlett et al., 1997; Sato et al., 1983). The role of previous comorbid conditions remains to be elucidated. As seen above, intertwined with the psychomotor sensitization hypothesis based mainly on psychostimulant actions, is a prominent and critical role for dopamine in the motivational effects of drugs of abuse; conversely, the allostatic-neuroadaptational position is that dopamine has a role in addiction, as many other transmitters, particularly for psychomotor stimulants, but not critical nor sufficient for the development of addiction to many drugs of abuse such as

opiates, alcohol, phencyclidine, and others (Pierce and Kumaresan, 2006). Moreover, for the allostatic neuroadaptational position the focus must be on motivational withdrawal, a key element of drug addiction, but not on physical aspects, markers of dependence (Koob and Le Moal, 2005a). Thus a chronic elevation of reward threshold (Koob and Le Moal, 2001) is viewed as a key element in the development of addiction and as setting up other sources of self-regulation failure and persistent vulnerability to relapse (protracted abstinence). The pathology of these neurocircuitries is the basis for the emotional dysfunction long associated with drug addiction and alcoholism in humans. This pathology largely persists into protracted abstinence, providing a strong motivational basis for relapse. This view that drug addiction and alcoholism are the pathology that results from an allostatic mechanism that usurps the circuits established for natural rewards provides a realistic approach to identifying the neurobiological factors that produce vulnerability to addiction and relapse.

4.4. A synthetic neurobiological model of addiction

The addicted brain is an end product of progressive dysregulations and pathophysiological changes in many structures and systems. Whether the disease and its characterized pathophysiology reflect the only causal toxic action of drugs or/and are an aggravation of previous vulnerabilities, reflecting psychopathological states and comorbidities from environmental and/or genetic origins, is not well known at the present time. This question merits more investigations in a near future and that will help to respond more accurately to the "why" of addiction. "What" is addiction, as a chronic disease, is described through a coherent and universally admitted list of symptoms as the result of a consensus in clinical research and the symptoms are a translation of a more better understood structure-function relationship. There is a structural logic that makes the diverse brain systems and regions linked together with both bottom-up and top-down organization, from physical symptoms to a damage to a self losing its will-power abilities (Bechara, 2005). The synthesis of the neural elements comprising most of the neurocircuitry models has several common elements. Most models include a key role for some component of reward usually involving the ventral tegmental area and the nucleus accumbens and frequently the central nucleus of the amygdala. Some have argued for a key role for basal forebrain suprastructure of the extended amygdala in this reward function. The ventral striatal-pallidal-thalamic loops have been hypothesized to play a key role in translating motivation in action (Kelley, 2004; Mogenson et al., 1980). The prefrontal cortex is hypothesized to have a key role in self-regulation and its pathology in control failures (Arnsten and Li, 2005; Dalley et al., 2004; Miller and Cohen, 2001) and in drug-induced reinstatement as the basal amygdala has a key role in cue-induced reinstatement. Finally, a key aspect of emotion and motivation involves the assessment of the environmental stimuli. The assessment is distributed through interconnected structures such as amygdala, ventral striatum, prefrontal cortex (Cardinal et al., 2002) that carry specific signals about past and future rewards (Schultz, 2000) and that control impulsive responses (Arnsten and Li, 2005). Stress neurocircuitry involving brain stem-basal forebrain loops is implicated not only in the negative affect associated with acute and protracted

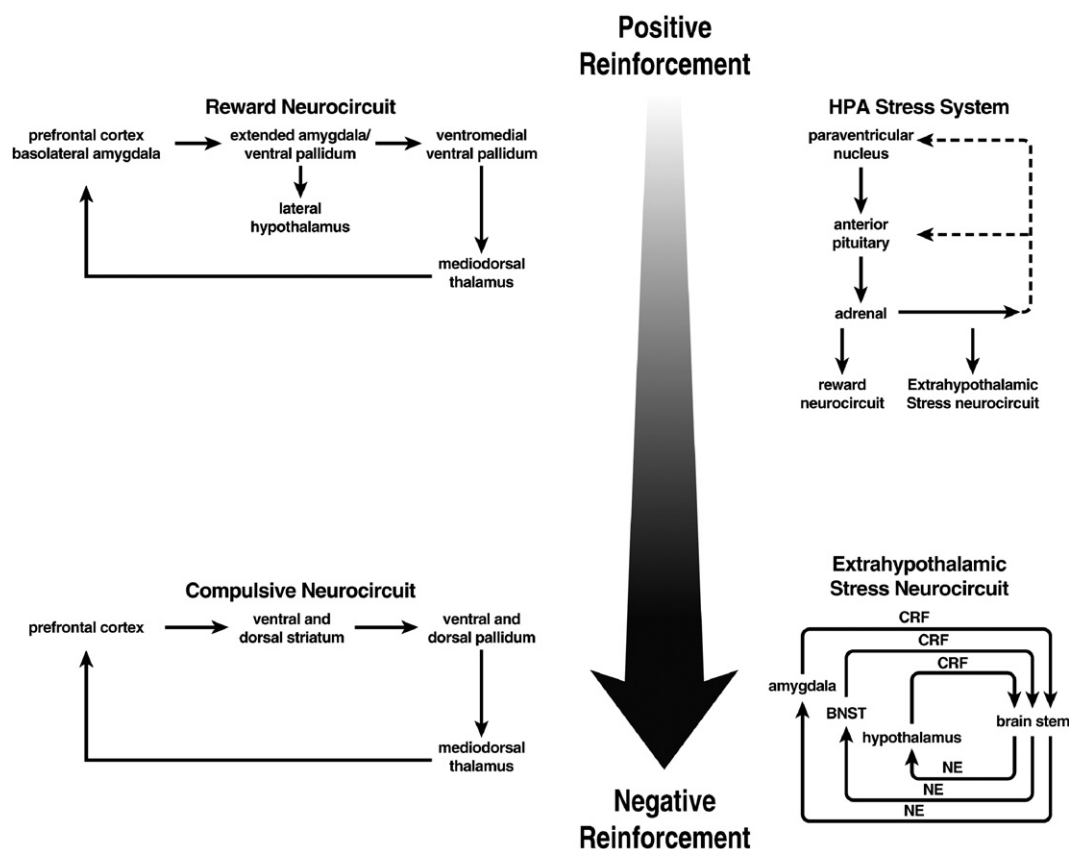


Figure 8 Brain circuits hypothesized to be recruited at different stages of the addiction process as it moves from positive to negative reinforcement. Top left: illustrates an increased in the activity of a brain reward system circuit with a focus on the extended amygdala and an increase in the drug- and cue-induced reinstatement circuit with a focus on the prefrontal cortex and basolateral amygdala which both drive positive reinforcement and impulsivity. Bottom left: illustrates a decrease in the brain reward circuit and an increase in the activity of circuits involved in driving negative reinforcement and compulsivity. Top right: the hypothalamo-pituitary-adrenal axis which feeds back to regulate itself, activates the brain reward systems, and facilitates the extrahypothalamic stress neurocircuit. Bottom right: brain stress circuits in feed-forward loops. DA: dopamine, BE norepinephrine, CRF: corticotropin-releasing factor, ENK: enkephalin, HPA, hypothalamo-pituitary-adrenal axis, B-End: beta-endorphin. Reproduced with permission from Koob and Le Moal (2005a).

abstinence from drugs of abuse but also in stress-induced relapse. In brief we speculate that pathophysiology including for most of the drugs a reward-stress circuit, a behavioral output/compulsivity circuit, and a drug- and cue-induced reinstatement or craving circuit, with a role for hippocampal regions, can be integrated into an overall heuristic model (Fig. 9). From this model further remarks must be made, especially concerning the transition from neuroadaptation to addiction and the correlative evolution in neurocircuitries changes. First, the acute reinforcing effects of drugs (binge/intoxication stage) involve action on the extended amygdala system, the ventral tegmental area, the arcuate nucleus, and ventral striatal-ventral pallidal-thalamic-cortical loops. Second, the symptoms of acute withdrawal, negative affects and increased anxiety associated with the negative affective stage involve decreases in function of the extended amygdala reward system and a recruitment of brain stress neurocircuitry. Third, the preoccupation/anticipation or craving stage involves key afferent projections to the extended amygdala, specifically the prefrontal cortex for drug-priming-induced reinstatement and the basolateral amygdala for cue-induced reinstatement; here it not still well understood how the activation of a compromised

prefrontal cortex executive functions important for reinstatement may be also responsible for elements of drug-induced craving. Fourth, we have seen (Fig. 2) that in the course of the development of addiction, changes occur in the way rewards are processed: initial activation of the extended amygdala and of the ventral striatal-ventral pallidal-thalamic loops representing positive reinforcement while the passage to addiction gives way to negative reinforcement with recruitment of the stress neurocircuitries; here it remains to understand how these hypothesized changes within the extended amygdala influence increased motivation for drug under the construct of negative reinforcement.

The present model suggests also that time is ripe to evaluate the role of dopamine systems in drug addiction. This role is limited. Much emphasis at the cellular and molecular levels has focused on neuroplasticity in the origin and terminal regions of the mesocorticolimbic dopamine system. The main reason is that this system has long been associated with the acute reinforcing effects of drug of abuse. However, the acute reinforcing effects of drug of abuse other than psychostimulants have been shown to be independent of the dopamine system: rodents continue to show rewarding

effects of heroin, alcohol and nicotine despite inactivation of the mesocorticolimbic dopamine system (Lavolette and van der Kooy, 2003; Le Moal et al., 1979; Pettit et al., 1984; Rassnick et al., 1993a,b). It is possible to argue for residual dopamine or for other dopamine system to explain these data, but a reasonable hypothesis is that elements independent of the dopamine systems can activate reward circuits outlined in Fig. 9. Other targets include interneurons that interact with either the cell bodies of the mesolimbic dopamine neurons or the medium spiny neurons within the nucleus accumbens and that are post-synaptic to the mesolimbic dopamine neurons. The list of the multitude of functions that have been attributed to the mesocorticolimbic system is long which role is more to facilitate responding to salient incentives, (Berridge and Robinson, 1998), to initiate action (Mogenson et al., 1980), to modulate several functions related to the propensity to respond (Salamone et al., 2005) than to mediate primary reward (Schultz, 2002). Nevertheless the simplistic view continues to be “drug reward = activation of the mesocorticolimbic dopamine system” and in consequence to orient most of the cellular and molecular studies on these neurons. Other circuits and targets must be investigated (Caine, 1998; Nestler, 2004).

5. Conclusions and perspectives for animal models

Drug abusers represent a heterogeneous group and pathways leading to addiction are diverse. Numerous sources of

vulnerability, from environmental stressors to genetics introduce large individual differences as regards the propensity to enter in the addiction cycle. Moreover, in the real life drug misuse is accompanied by the existence of a high level of comorbid psychopathological conditions and of poly-drug usage. Addiction corresponds to the last stage of a process; it is a chronic relapsing disease. The symptoms that constitute the definition reflect a complex neuropathology on which many models refer. The pathophysiological processes leading to the transition from use to misuse and finally (for some users) to addiction has been presented as the course of a spiraling distress-addiction cycle that integrates different conceptual perspectives, from preoccupation/anticipation, to binge/intoxication, to withdrawal/negative affect. The neuroadaptive hypotheses underlying the pathophysiological processes are based on the concept of the development of an opponent process leading to a coneradaptation that solicits many neuronal systems in an allostatic state. This perspective is based upon clinical and experimental observations. In experimental research based on animal models the confusion between drug self-administration in laboratory animals and addiction has lasted too long and is at the origin of unfortunate misinterpretations. Again, addiction is a strictly defined medical condition, a disease with generally admitted symptoms and deficits not present after current self-administration protocols, even in the long-term. A closely approximating model must, for instance, demonstrate that a large availability or access to drug produces, after a certain point, an uncontrollable escalation in drug intake, profound depression of the reward system (Ahmed et al., 2002; Ahmed and Koob,

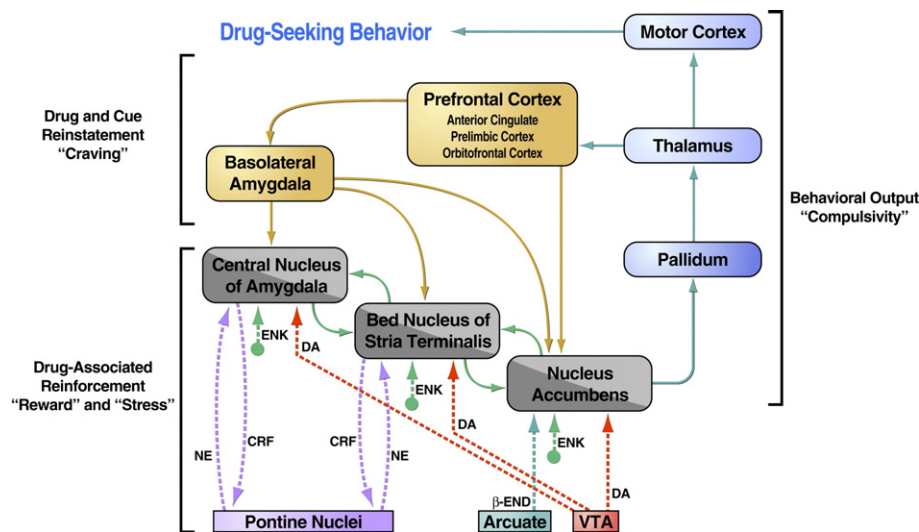


Figure 9 The three major neurocircuits that underlie addiction. A drug-reinforcement circuit is comprised of the extended amygdale including the central nucleus, the bed nucleus of the stria terminalis, and the transition zone in the shell of the nucleus accumbens. Multiple chemical systems issued from mesencephalic and pontine nuclei modulate this circuit: dopamine (DA), enkephalin (ENK), beta-endorphin (B-END), for reward, corticotrophin releasing factor (CRF) and norepinephrin (NE) for stress. This circuit integrates rewarding stimuli or stimuli with positive incentive salience and also aversive stimuli or stimuli with negative aversive salience. During the first stages of drug intoxication, valence is weighted on processing rewarding stimuli, and, as dependence develops, aversive stimuli come to dominate function. A drug and cue induced reinstatement circuit is comprised of the prefrontal cortex (drug induced craving) and basolateral amygdala (cue induced craving). A drug seeking circuit (compulsivity) is comprised of the nucleus accumbens pallidum-thalamus-prefrontal cortex loop. The three circuits are, of course, interconnected and neuropathology includes structures from the pons and mesencephalon to frontal cortex. The hippocampus, which mediates specific learning, is also implicated. Reproduced with permission from Koob and Le Moal (2005a).

1998) and propensity to relapse after a long period of withdrawal when drug or related cues are present (Deroche et al., 1999). More recent models have allowed the development of addiction-like compulsive behaviors (Vanderschuren and Everitt, 2004). These models do not take into account a possible individual differential vulnerability (see above, drug-centered versus individual centered approaches). Recently (Deroche-Gamonet et al., 2004), it has been shown that after a prolonged self-administration period, rats displayed behaviors resembling those considered as hallmarks of dependence (DSM IV), but that individual differences appeared with a gradation from the most addicted animal to the resilient one. The rats developed zero, one, two or three (the most addicted) addiction-like compulsive behaviors, i.e., i) difficulty for limiting/stopping nose-poking for drug during no-drug periods, ii) substance use continued despite its harmful consequences: drug delivery associated with shock punishment signaled by a cue light, iii) extremely high motivation to take the drug as demonstrated by a progressive-ratio schedule. Moreover addicted rats showed after a long period of abstinence a propensity to relapse after a priming dose of cocaine or after presentation of a drug-associated stimulus. A better description of the clinical features of drug addiction, a proper definition of the disease, progresses in understanding the pathophysiological mechanisms must open the road to more appropriate experimental investigations.

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