ACTUALIZACION POR TEMAS

Neurobiology of addiction neuroanatomical, neurochemical, molecular and genetic aspects of morphine and cocaine addiction

PART I

Philippe Leff*
Ma. Elena Medina-Mora*
Juan Carlos Calva*
Armando Valdés*
Rodolfo Acevedo*
Aline Morales
Mayra Medécigo*
Benito Antón*

Summary

Addiction is a serious clinical and social problem that impacts public health organizations in many countries. From a medical viewpoint, addiction is a complex neurobiological phenomenon that affects different functional and molecular processes in specific areas of the mammal brain including human. Animal models of addiction have extensively used pharmacological paradigms of drug self administration with the aim of investigating the addictive properties of psychotropic substances such as morphine, heroine and cocaine. Thus, studies on these animal models have identified that addictive properties of these substances depend upon their pharmacological actions for altering the specific neural functions of the mesocorticolimbic dopaminergic circuitry. Specific electrophysiological, neurochemical and genomic alterations in the mesocorticolimbic dopaminergic pathway have been identified during the development and long-term consolidation of complex behavioral states related to drug dependence and reward. This work reviews the current information related to the major electrophysiological and neurochemical alterations that have been observed in the dopaminergic mesocorticolimbic circuitry during the addictive processes of morphine, heroin and cocaine.

Key words: morphine, cocaine, mesocorticolimbic system, dopamine, neuron, opioid receptor, neural transmission, addiction.

** Laboratorio de Neurobiología Molecular y Neuroquímica de Adicciones, División de Investigaciones Clínicas, Instituto Mexicano de Psiquiatría. Calz. México-Xochimilco N°. 101. México, D.F. C.P. 14370.*

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Resumen

La adicción representa un importante problema de salud a nivel clínico y social en múltiples países. Desde el punto de vista médico, la adicción es un complejo fenómeno neurobiológico que afecta diversos procesos funcionales y moleculares en diferentes áreas específicas del cerebro de los mamíferos, incluyendo al humano. Diversos modelos animales sujetos a esquemas de autoadministración farmacológica han sido estudiados con el objeto de investigar las propiedades adictivas de múltiples sustancias psicotrópicas, como es el caso de la morfina, la heroína y la cocaína. Estos estudios han concluido que los efectos psicoadictivos de estas sustancias se deben principalmente a la alteración de la actividad neuronal del sistema de transmisión dopaminérgico mesocorticolímbico. Este sistema neuronal sufre cambios funcionales a nivel electrofisiológico, neuroquímico y genómico, que participan en forma concertada en el desarrollo y establecimiento a largo plazo, en el reforzamiento y en la recompensa al consumo de las sustancias adictivas antes mencionadas. Este trabajo describe el cuerpo de conocimientos actuales relacionados con los cambios funcionales que se desarrollan y establecen durante el fenómeno adictivo a la morfina, la heroína y la cocaína.

Palabras clave: Morfina, cocaína, sistema mesocorticolímbico, dopamina, neurona, receptor opioide, trasmisión neural, adicción.

Introducción

Addiction is known as the dependence on substances of abuse (American Psychiatric Association, 1993) characterized by a chronic and recurrent neurophysiologi-

cal alteration associated with progressive changes in behavioral states associated with compulsive seeking and intake of psychotropic substances. These behaviors are frequently associated with a loss of control of limiting intake of such substances with an emergence of a negative emotional state (e.g., anxiety, irritability and dysphoria) when access to the drug is prevented (Benowitz, 1993; Koob et al., 1998). Drug addiction is a complex phenomenon with direct impact on the individual and social welfare. Although some aspects of drug addiction can occur relatively rapidly in response to acute administration of a drug of abuse, most changes in brain function associated with addiction gradually occur in response to prolonged drug exposure. These gradually developing changes may persist for a long period of time after cessation of drug administration. The adaptive changes that occur in brain function concern those biological effects that induce specific signs and symptoms that characterize an addictive syndrome such as tolerance, sensitization, dependence and withdrawal. Tolerance is defined as a reduced effect upon repeated exposure to a constant drug dose, or the need for an increased dose to maintain the same initial effect. Sensitization, or "reverse-tolerance", describes an opposite effect, in which a constant drug dose elicits increasing effects. Dependence is defined as the need for continued drug exposure to avoid a withdrawal syndrome, characterized by specific physical or psychological disturbances when drug is withdrawn. Therefore, the physical and psychological disturbances developed during addiction correlate with the development of progressive neuroadaptive changes in specific neuronal circuitry during prolonged drug exposure. The gradual development and long-term consolidation of persistent functional adaptations in the brain during drug addiction suggest its key modulatory role in mediating the addictive phenomena. Therefore, a central question to understand the neurobiological mechanisms involved in the development of the addictive phenomenon is the one related to the search for specific cellular, electrophysiological and neurochemical adaptive processes that occur in parallel to the development and consolidation of specific addictive behaviors. Moreover, drug addiction implies a drug-induced neural plasticity, which is a useful model for investigating the neural mechanisms involved in brain plasticity. Furthermore, neural adaptations that occur in the brain during addiction may be generated and encoded at a cellular level with long-term consolidated molecular memory (figure I). In summary, from a pharmacological viewpoint, addiction could

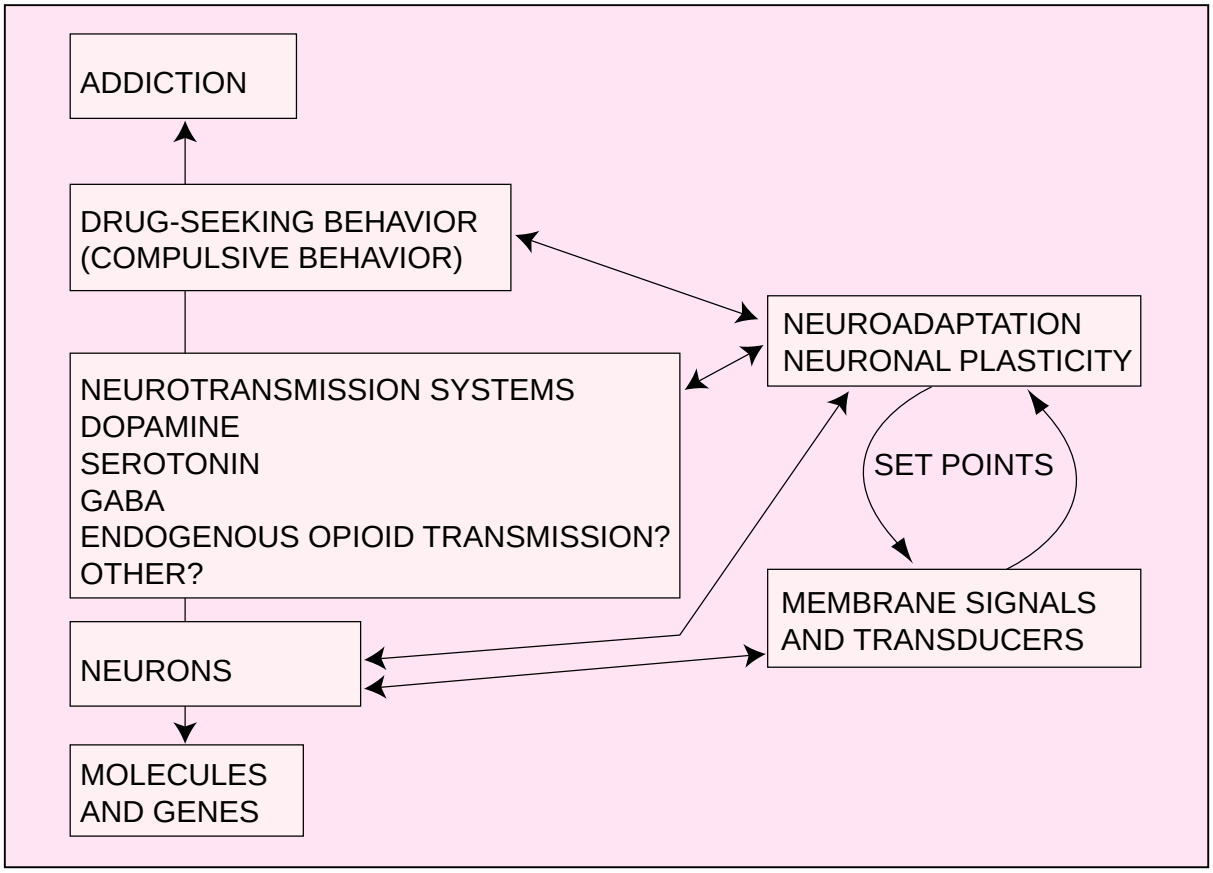

Figure 1. Schematic diagram showing the different levels of experimental approaches in the study of drug addiction: the role of neuroadaptive processes. Molecular and cellular neuroadaptive mechanisms contribute to the development and establishment of drug addiction. All these neuroadaptive mechanisms (e.g., neurotransmission systems, membrane signals and chemical transducers systems; intracellular molecules and genes) are known to contribute to drug seeking and compulsive behavior. These molecular and neuronal mechanisms acting at different levels of a spiraling cycle in the development of drug dependence produce long term neuroadaptive changes in several neurotransmission systems that enhance the establishment of the addictive phenomena (Adapted from Koob & Le Moal, 1997, Koob et. al., 1998; and modified by the authors of this publication).

then be seen as a complex drug-altered behavioral state that implicates the development and presence of other drug-intake reinforcing behaviors, such as tolerance, sensitization and dependence, which are enhanced by an initial acute exposure and subsequent repeated administration of an addictive substance. The present chapter is focused on a description of the current knowledge of the major neuroanatomical, electrophysiological and chemical changes that occur during addiction to opiates and cocaine, one of the most highly abused drugs in humans.

Neuroanatomical and neurochemical and neurochemical changes in experimental models of cocaine addiction

A major goal of current research in the field of the neurobiology of addictions is to study the functional adaptations that occur in specific neuronal groups of the brain areas during the development and establishment of different behavioral alterations observed in addictive syndromes. Most of the studies related to these research topics have been approached in animal models, thus enabling the identification of specific biological mechanisms implicated in the development and establishment of the addictive phenomena (for a comprehensive review see Koob et al., 1998; Nestler, et al., 1993, Nestler and Aghajanian, 1997). Although the experimental models of drug abuse developed in such animals do not completely simulate the pharmacological and environmental conditions which favor the development and establishment of the addictive process in humans, most of the experimental approaches in animal models have been devoted to identify in the brain, the specific cellular and molecular events that are responsible for the development and establishment of addictive phenomena (Koob et al., 1998). In line with this experimental work, several pharmacological studies have documented the importance of two neuronal dopaminergic projecting systems of the mammal's brain, as the neuroanatomical loci where most drugs of abuse exert either directly or indirectly their pharmacological reinforcing actions (e.g., morphine, heroin, cocaine and d-amphetamines [Woolverton and Johnson, 1992]. The first of these neuronal pathways is the nigrostriatal system, which is formed by neuronal groups that send efferent dopaminergic projections from the substantia nigra (SN) to the striatum. The second dopaminergic pathway is composed by both neuronal groups localized in the ventro tegmental area (VTA) of the mesencephalon, that send an abundant network of efferent fibers that make synaptic connections with neurons localized in the nucleus accumbens (NAc), olfactory tubercle (OT) , prefrontal cortex (PFCX) and amygdaloid complex (Amg). This latter dopaminergic circuitry is the main neural substrate implicated in the reinforcing actions of most drugs of abuse, including morphine, heroin and cocaine. It has been demonstrated that these substances have the ability to modify the chemical and molecular functioning of these dopaminergic neurons through distinct functional mechanisms. For example, cocaine inhibits the membrane dopamine protein transporter thus inhibiting the re-uptake of synaptic dopamine to cytoplasmic neuronal compartments (Nestler, 1996; Koob et al., 1998). Thus, the potent reinforcing actions of cocaine are directly related to its capacity of producing a sustained increase of synaptic concentration of dopamine. In support of these neurochemical findings there is pharmacological data of intravenous cocaine self-administration studies coupled to *in vivo* perfusion of mesolimbic areas with microdialysis probes. For instance, some studies have shown that a chronic schedule of self-infused cocaine produces a sustained increase of neuronal efflux of dopamine in dopaminergic synaptic terminal fields of the NAc (Koob et al., 1998; Pettit and Justice, 1989). It has also been demonstrated that the alteration of synaptic levels of dopamine correlate in parallel with the activation of specific dopaminergic receptors (e.g., Dl, D2 and D3) localized in postsynaptic neurons in the NAc. Moreover, the dopamine receptor activation is the initial membrane event that triggers a significant increase in neuronal excitability and over activation of the dopaminergic mesocorticolimbic system, an electrophysiological alteration that is finally translated into the expression of behavioral "repertoires" associated to cocaine addiction (Koob and Le Moal, 1997; Koob et al., 1998). Furthermore, other pharmacological studies have shown that the intraventricular injection of selective dopaminergic receptor antagonists in the rat brain reduces the reinforcing properties of cocaine self-administration (Caine et al., 1995; Epping-Jordan, 1998). Similar results have been observed when dopaminergic neurons in either the ventro tegmental area or nucleus accumbens are selectively destroyed with the neurotoxin 6-hydroxydopamine (6-OHDA) (Roberts et al., 1980; Koob et al., 1998). Electrophysiological studies performed in animal models of cocaine self-administration have demonstrated that the nucleus accumbens is a key brain region where important neurochemical changes occur in association with specific behavioral patterns of drug reinforcement (Chang et al., 1994; Carelli and Deadwyler, 1996; Peoples et al., 1997). For example, *in vivo* extracellular electrical recordings in the nucleus accumbens of animals exposed to intravenous cocaine selfadministration, have identified distinct patterns of neuronal responses to cocaine within this structure (Carelli and Deadwyler, 1996; Koob et al., 1998). A first group of neurons are selectively depolarized a few seconds before cocaine infusion, meaning that neuronal anticipatory responses occur as a trigger mechanism for the initiation of drug intake (e.g., increase in the frequency of neuronal triggering). A second group of neurons change their firing rate after the exposure to the pharmacological paradigm of cocaine self-infusion, which suggests that these cells might be responsible for the reinforcing effects of cocaine (Carelli and Deadwyler, 1996). Furthermore, a third group of neurons seems to change its firing rate during the time-intervals among sessions of cocaine self-infusion (Peoples and West, 1996). Finally, a fourth pattern of activation of electrical firing has been observed in a group of dopaminergic neurons referred to as "cocaine-specific cells" which are only activated when cocaine is self-administered (Carelli and Deadwyler, 1996). In line with these data, it is intriguing that these latter subset

of neurons also change their electrical excitability in response to sensory stimuli such as light and sound, a kind of stimuli that is routinely used as conditioning reinforcers for cocaine administration in addictive pharmacological paradigms of self-infusion of this drug in animal models (Carelli and Deadwyler, 1996). Likewise, this kind of sensory stimuli has been observed to be strong elicitors of cocaine "craving" in human addicts (Carelli and Deadwyler, 1996; Koob et. al., 1998). Therefore, the existence of specific dopaminergic neurons in the nucleus accumbens has been postulated as a key cellular target for mediating stimuli conditioned drug responses. Overall, all these experimental findings also support the existence of specific neuronal groups within the nucleus accumbens, which functionally modulate several drug reinforcing responses to cocaine as well as the behavioral state of "seeking" for this drug in human beings (Koob et al., 1998; Robbins and Everitt, 1999).

The reinforcing properties and the long-term neuroadaptations that occur in animal models subjected to cocaine self-administration paradigms depend not only on the capacity of this drug to increase the extracellular dopamine concentration in the nucleus accumbens but also on the cocaine's capacity to induce alterations in the excitability of dopaminergic neurons localized in additional drug reinforcing areas of the mammal brain. So far, experiments using recombinant DNA techniques to generate the "knock-out" of specific genes that modulate the dopaminergic transmission system, have provided further evidence of the neurochemical basis of cocaine reinforcement (Giros, et al., 1996). Thus, some interesting observations have been observed in homozygous transgenic mice strains in which the specific gene coding for the membrane dopamine transporter protein has been altered for its expression via homologous DNA recombination techniques (Giros et al., 1996). On the one hand, these studies have shown that cocaine is no longer able to change the extracellular baseline levels of dopamine in the brain rewarding areas of the mouse. On the other hand, there has also been observed in cocaine self-administration paradigms in these transgenic animals a lack of cocaine's capability to generate specific behavioral changes such as hyperlocomotion and motor stereotypes, commonly seen in animal models of drug self-administration. Moreover, these latter results suggest that the negative modulation on the functional activity of the membrane dopamine transporter by cocaine, represent a critical neurochemical event through which cocaine is capable of inducing and perpetuating its characteristic compulsive-seeking behavior in addictive mammals including the human. However, the existence of additional and more complex neurochemical mechanisms implicated in the reinforcing actions of cocaine has been suggested (Rocha et al., 1998), since paradoxical results have been observed when the dopamine transporter-deficient mice are still able to be trained to self-administer cocaine regardless of the high levels of extracellular dopamine found in dopaminergic terminal fields, a neurochemical alteration that is also seen in non-transgenic control animals exposed to cocaine self-administration.

Neuroanatomic and neurochemical changes in animal models of morphine and heroin addiction

The reinforcing properties of opiates are mediated through the capacity that these drugs have for altering specific functions of the same dopaminergic circuitry modulated by cocaine, although the pharmacological profile of opiates probably involve additional neural sites of interaction (Koob and Bloom, 1988; Koob et al., 1998). In such context, it has been well documented that the reinforcing actions of opiates such as morphine and heroin, are exerted via alterations in the activity of the dopaminergic circuitry in drug rewarding brain areas of mammals such as the ventral tegmental area, nucleus accumbens, amygdaloid complex and prefrontal cortex (Koob and Bloom, 1988; Koob et al., 1998; Shoab and Spanagel, 1994). The prefrontal cortex, as a neuroanatomical part of the mesocorticolimbic system, provides a major excitatory projection to the nucleus accumbens, whereas this latter structure in turn influences this cortical area by a poly-synaptic feedback circuitry. Both regions receive dopaminergic projections from the ventral tegmental area, where morphine and heroin mediate their behavioral reinforcing actions. In addition, the prefrontal cortex is also known as a relevant cortical area for processing cognitive functions such as learning and memory (Berendse et al., 1992; Brog et al., 1991; Giacchino and Henricksen, 1998).

Similar to cocaine, morphine and heroin are also intravenously self-administered by animals, so that systemic or central administration of competitive opiate antagonists will affect opiate self-administration by reducing their reinforcing properties (Di Chiara and North, 1992; Koob and Bloom, 1988). Thus, pharmacological studies have demonstrated that reinforcing actions of morphine and heroin are largely mediated by specific activation of the mu opioid receptor subtype in the ventral tegmental area, since administration of selective antagonists for this receptor decreases reinforcing properties of opiates in a dose-dependent manner (Negus, et al., 1993). Moreover, immunohistochemical studies (Mansour et al; 1987, 1988, 1995) have shown a high expression of the mu opiod receptor in mesocorticolimbic areas implicated in drug reinforcement. In addition, experimental approaches using recombinant DNA techniques commonly used to "knock out" specific genes, have demonstrated that the reinforcing actions of morphine and heroin can be completely abolished in an homozygous strain of mice-deficient for the mu opoid receptor gene (Matthes et al., 1996; Kieffer, 1999). These data provided the first evidence that the mu opioid receptor is the key molecular entity for mediating the addictive actions of opiates such as morphine and heroin.

In support of the central modulatory role of the mu opioid receptor subtype in opiate addiction it has been demonstrated that local application of non-selective mu opioid antagonists (e.g., naloxone and naltrexone) into either the ventral tegmental area or the nucleus accumbens reduces the reinforcing properties of opiates as demonstrated by a significant reduction of drug-intake in animals subjected to paradigms of heroin self-administration (Koob et al., 1998). Furthermore, it has

also been shown that the local administration of either endogenous (e.g., b-endorphin) or synthetic (e.g., DAMGO) agonists of the mu opioid receptor into drug rewarding brain areas increases the reinforcing actions of morphine and heroin self-administration (Vacarrino et al., 1985; Corrigall et al., 1988, 1992; Shippenberg et al., 1992) Additional results have shown that the pharmacological antagonism of the mu opioid receptor induces withdrawal-like behavioral responses when morphine and heroin administration is acutely suppressed (Nestler, 1992, 1996; Widnell et al., 1996).

Additional electrophysiological and pharmacological studies have shown that morphine induces simultaneously an increase in both the excitability of dopaminergic neurons and the synaptic outflow of baseline dopamine release in the ventral tegmental area (Matthews et al., 1984; Chang et al., 1997). In line with these studies are the findings demonstrating that the abrupt withdrawal of either morphine or heroin self-administration induces important neurochemical and electrophysiological changes that significantly decrease both the dopaminergic (Diana et al., 1993; Weiss et al., 1996; Koob et al., 1998) and the endogenous opioid neurotransmission function (Di Chiara and North, 1992; Self and Nestler, 1995) in drug rewarding areas of the rodent brain. Furthermore, several reports have shown that the reinforcing actions of morphine and heroin in the nucleus accumbens remain after the chemical destruction of dopaminergic projections of the ventral tegmental area and nucleus accumbens with either 6-OHDA (Roberts et al., 1980) or kainic acid (Zito et al., 1985). These latter results support the hypothesis that different neurochemical circuitry and molecular events could be involved in modulating the motivational and behavioral reinforcing actions of opiates (Koob and Bloom, 1988). This hypothesis is supported by several electrophysiological findings that demonstrate the existence of distinct neuronal populations with different electrical activity responses after self-administration of morphine and heroin (Chang et al., 1997; Kiyatkin and Rebec, 1996, 1997; Peoples et al., 1997). For instance, studies of single unit recordings of neurons in the nucleus accumbens and prefrontal cortex of animals exposed to intravenous self-administration of heroin have shown that activity of distinct groups of neurons change before, during and after the infusion period of heroin (Chang, et al., 1997). Thus, on the one hand, one group of neurons increases its firing rate a few seconds before the opiate infusion (heroin-anticipatory excitatory responses) and another set of neurons discharge when the administration of the opiate is withdrawn (post-heroin excitatory responses). On the other hand, a different group of neurons show a decreased firing rate seconds before the opioid infusion (heroin-anticipatory inhibitory responses) and finally, there is a fourth group of neurons that show a decreased firing rate during opiate withdrawal. Thus, besides the dopaminergic transmission, all these studies may suggest the existence of additional complex interactions among distinct neuronal transmitter systems besides the functional modulation of the reinforcing actions of these drugs of abuse. Additional multidisciplinary studies will be necessary in order to obtain a better understanding of the cellular and functional basis of the addiction to opiates and non opiate drugs of abuse.

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RESPUESTAS DE LA SECCION AVANCES EN LA PSIQUIATRIA

Autoevaluación

1. **d**
2. **c**
3. **c**
4. **b**
5. **a**
6. **d**
7. **e**
8. **b**
9. **c**
10. **a**
11. **b**
12. **a**
13. **e**