Progress in Neurobiology 86 (2008) 1–21

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

β-Endorphin and drug-induced reward and reinforcement

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ARTICLE INFO

Article history:
Received 9 April 2008
Accepted 11 June 2008

Keywords:
β-Endorphin
Dopamine
Reward
Addiction
Drugs
Reinforcement

ABSTRACT

Although drugs of abuse have different acute mechanisms of action, their brain pathways of reward exhibit common functional effects upon both acute and chronic administration. Long known for its analgesic effect, the opioid β-endorphin is now shown to induce euphoria, and to have rewarding and reinforcing properties. In this review, we will summarize the present neurobiological and behavioral evidences that support involvement of β-endorphin in drug-induced reward and reinforcement. Currently, evidence supports a prominent role for β-endorphin in the reward pathways of cocaine and alcohol. The existing information indicating the importance of β-endorphin neurotransmission in mediating the reward pathways of nicotine and THC, is thus far circumstantial. The studies described herein employed diverse techniques, such as biochemical measurements of β-endorphin in various brain sites and plasma, and behavioral measurements, conducted following elimination (via administration of anti-β-endorphin antibodies or using mutant mice) or augmentation (by intracerebral administration) of β-endorphin. We suggest that the reward pathways for different addictive drugs converge to a common pathway in which β-endorphin is a modulating element. β-Endorphin is involved also with distress. However, reviewing the data collected so far implies a discrete role, beyond that of a stress response, for β-endorphin in mediating the substance of abuse reward pathway. This may occur via interacting with the mesolimbic dopaminergic system and also by its interesting effects on learning and memory. The functional meaning of β-endorphin in the process of drug-seeking behavior is discussed.

Contents

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doi:10.1016/j.pneurobio.2008.06.003

1. Introduction

Involvement of the opioid system in drug-induced reward and reinforcement has been intensively investigated over the past few decades. Most of these studies employed pharmacological means, and examined involvement of opioid receptors in these phenomena. However, an exclusive role for a specific opioid in the behavioral effects of addictive drugs could not be assessed, since endogenous opioids bind to the various opioid receptors with differing affinities (Goldstein and Naidu, 1989). Long known for its analgesic effect, the opioid β-endorphin is now known to induce euphoria, and to have rewarding and reinforcing properties. In this review, we will summarize the present neurobiological and behavioral evidences that support involvement of β-endorphin in drug-induced reward and reinforcement. The studies described herein employed diverse techniques, such as biochemical measurements of β-endorphin in various brain sites and plasma, and behavioral measurements of drug self-administration, conditioned place preference and intra-cranial self-stimulation. The behavioral measurements were conducted following elimination (via administration of anti-β-endorphin antibodies or using mutant mice) or augmentation (by intracerebral administration) of β-endorphin. We will focus mainly on the relationship of β-endorphin and cocaine, and briefly touch on the relationship of β-endorphin and other non-opiate substances of abuse, such as ethanol, nicotine and tetrahydrocanabinol (THC).

2. Drug addiction

2.1. Characterization of the addiction process

Drug dependence is a major health problem which afflicts large segments of the world population. Investigation of neurochemical circuits affected by chronic exposure to drugs of abuse has advanced our understanding of this dependence. Addictive drugs are thought to activate brain circuitry that normally mediates natural rewards, such as food or water. GABAergic, dopaminergic, glutamatergic, and cholinergic systems within the mesocorticolimbic circuitry are involved in both natural reward function and drug addiction (Ikemoto and Wise, 2004; Kelley and Berridge, 2002).

The neuronal circuits and substrates involved in the initial stages of drug abuse are not necessarily those involved in the maintenance, extinction, or relapse phases of drug addiction. Furthermore, neurobiological and contextual processes may differentially contribute to drug consumption that occurs during various phases of the addiction process. For example, using the self-administration paradigm (see Section 2.2.3), the decreased reinforcing effect of a drug following pharmacological treatment manifests as a decreased demand for the drug during the initiation phase. However, the same pharmacological treatment during the stable intake (maintenance) phase causes the opposite behavioral response, i.e. an extinction-like effect and increase in lever responses (for behavioral, physiological, and neurochemical aspects of addiction see Everitt and Robbins, 2005; Grinspoon and Bakalar, 1985; Koob and Le Moal, 2005; Lu et al., 2007; Shaham and Hope, 2005; Shalev et al., 2002; Vanderschuren and Everitt, 2005; Volkow et al., 2004a; Weiss, 2005). Phases of addiction are schematically presented in Fig. 1, based on the subjective response of addicts and the behavioral response of experimental animals.

A primary experience with a drug is defined as the initiation phase. During this phase, continuation of drug use depends on the local culture, genetic vulnerability and subjective (pleasant or unpleasant) effects of the drug. Positive subjective effects, such as euphoria, ecstasy, or relaxation, may account for the reinforcing effects of addictive drugs, and can bring about a gradual escalation in drug use. The neuronal reward system, including brain regions as the ventral tegmental area, nucleus accumbens, and prefrontal cortex, is probably involved in the development of the initiation phase of addiction. An increase in the reward system activity is accompanied by a gradual rise in stress system functioning, including the amygdala, bed nucleus of stria terminalis, and hypothalamus (Everitt et al., 2001; Gerrits et al., 2003; Koob and Le Moal, 2001).

Transition from the initiation to the maintenance phase of drug dependency is not sufficiently understood. Yet it is accepted that the compulsive patterns of seeking, obtaining, and using drugs during the maintenance phase are a defining characteristic of drug addiction (Vanderschuren and Everitt, 2005). Use of addictive drugs on a regular basis during the maintenance phase can cause a psychic and biological dependence, which is characterized by heightened craving for the drug. Craving leads to compulsive behavior and continued drug use, to eliminate unpleasant withdrawal symptoms. During the maintenance phase, the cortico-frontal-cingulate circuit becomes increasingly prominent (Childress et al., 1999; Kilts et al., 2001; Wexler et al., 2001), and is accompanied by activity of the stress system (Grant et al., 1996). During this phase, the desire for the drug remains high, although the main neuronal system involved is not that of reward, and drugs are no longer pleasurable. Recently, drug addiction was suggested to involve continual recruiting of anti-reward systems, such as corticotropin-releasing factor (CRF), norepinephrine and dynorphin, concurrently with the decrease in

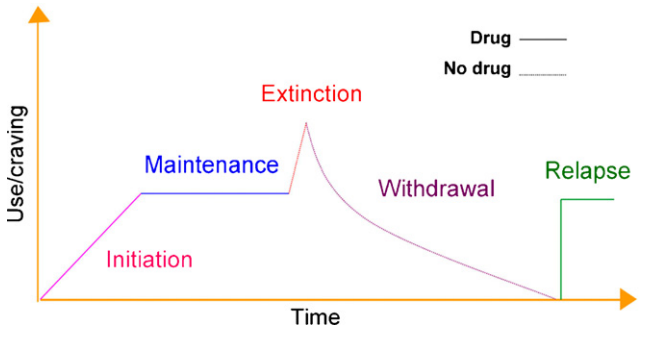

Fig. 1. Schematic diagram of the addiction process. Time course of drug use/craving is presented. The initial period of drug intake (i.e. initiation) is manifested by a gradual increase in drug consumption until a stable level is achieved (i.e. maintenance). Discontinuation/extinction of drug intake causes a high demand/craving for the drug, which declines along time (i.e. withdrawal). During abstinence the former addict is still prone to relapse following re-exposure to the drug, drug-associated cues or stress. Addiction levels return to their former degree of intake (i.e. relapse).

function of normal reward-related neurocircuitry (Koob and Le Moal, 2005). Anti-reward circuits may produce aversive or stress-like states during the process of addiction (Koob and Le Moal, 2005), and provide a robust negative reinforcement that defines compulsive drug-seeking behavior and addiction.

Drug detoxification in human subjects is also manifested by craving. Using behavioral paradigms in experimental animals, drug detoxification is characterized by high instrumental response, which might be due to frustration, stress, or extinction of a trained habit (Mason, 1983; Romero et al., 1995). Usually, cessation of drug intake is immediately followed by withdrawal symptoms which last from several days to 3 weeks. Withdrawal symptoms are generally the opposite of the drug's positive effects and may be attributable to the system's effort to maintain homeostasis. Following the first period of abstinence, the physiological symptoms of withdrawal cease, but an intense desire for the drug is still high in humans (Gorelick et al., 2005; O'Brien, 2005). Therefore, relapse to drug use is common among former addicts, and is the most difficult challenge in addiction therapy (O'Brien, 2005). Relapse often occurs following such incidents as a stressful episode, re-exposure to the drug via priming effects with drugs and other reinforcers, or exposure to a drug-associated environmental cue (deWit, 1996; Sinha, 2001). In preclinical studies, neural systems involved in reinstatement (see Section 2.2.4) to different drugs, such as cocaine and heroin are partially dissociable, with some overlap among the brain sites that mediate reinstatement induced by drug priming, associated cues, and stress (Bossert et al., 2005). Drug and cue-induced reinstatement of drug seeking are mediated by the mesocorticolimbic dopaminergic system via its various projections (Shaham et al., 2003). In cocaine-trained rats, the brain regions implicated in drug-induced reinstatement are the medial prefrontal cortex and nucleus accumbens core and shell, whereas the critical sites for cue-induced reinstatement (mostly via light and tone cues) are the basolateral amygdala and the prefrontal cortex. Stress-induced reinstatement (using foot shock as a stressor) involves CRF and noradrenalin in the bed nucleus of the stria terminalis and the central nucleus of the amygdala (Bossert et al., 2005; Shaham et al., 2003; Shalev et al., 2002).

A recent study provides evidence from laboratory animals suggesting that the onset of relapse following withdrawal from cocaine is delayed and that craving does not decay, but rather "incubates", i.e. increases progressively, over a 2-month withdrawal period (Grimm et al., 2001). In this study, cue-induced reinstatement intensified linearly over the 2-month period, suggesting that the individual is most vulnerable to relapse at times well beyond the acute phase of drug withdrawal. However, while the incubation of responses to cocaine cues is a long-lasting phenomenon (up to a 6-month period of withdrawal), it is not permanent (Lu et al., 2004). In addition, the neuronal substrates underlying the incubation process are not entirely clear, although recently (Lu et al., 2007) involvement of central amygdala glutamate was shown in this process. Furthermore, brain-derived neurotrophic factor (BDNF) levels in the ventral tegmental area, nucleus accumbens and amygdala progressively increased following cocaine withdrawal (Grimm et al., 2003), suggesting involvement of BDNF in synaptic modifications that underlie enhanced responsiveness to cocaine cues after prolonged withdrawal periods.

2.2. Behavioral assessment of drug-induced reinforcement

Animal models for drug dependence, wherein characteristic aspects of human drug dependence can be mimicked, have provided a useful tool to study the neurobiological substrates underlying the dependence-creating properties of drugs of abuse. Several animal models based on operant conditioned behavior (see below), have been used to monitor the reinforcing and rewarding effects of addictive drugs. The underlying principle of operant conditioning is that consequences control behavior. An animal performs since it is reinforced for doing so. Reinforcement can be positive (food, water or addictive drugs) or negative (electric shock that can be avoided by making the correct response). Animals learn to obtain rewards and avoid punishment by responding correctly.

2.2.1. Intracerebral electrical self-stimulation

This operant technique allows subjects to perform a specific task, such as lever pressing, in order to self-administer a weak electric current to discrete brain areas via an intracerebral electrode (Olds and Milner, 1954). The underlying assumption is that certain brain areas contain central reward pathways. When an animal presses the lever, a particular cluster of neurons is stimulated. The electrical activation causes release of neurotransmitters in the brain region, which in turn mediate the rewarding effect. Intracranial drug administration can be used to localize brain areas where drugs of abuse initiate their habit-forming actions (Tzschentke, 2000; Wise and Hoffman, 1992) and to characterize the rewarding effects of drugs (Maldonado, 2002). A decrease in the electric current of the threshold for intracranial self-stimulation following exposure to a particular drug is interpreted as an enhancement of the brain reward mechanism upon exposure to the drug.

2.2.2. Conditioned place preference

Place conditioning is useful for evaluating the reinforcement potential of psychotrophic drugs (Mucha et al., 1982). This procedure relies on a classical conditioned association between the effect of the drug and the environment. In this technique, animals are given several conditioning trials in which either a drug or a vehicle is injected. Following the injection, the subject is confined to one of two sensually distinguished compartments of an apparatus. Drug and vehicle injections are always paired with different compartments, so that the animal can associate drug-induced changes it experiences with environmental cues provided by the apparatus. During test sessions, animals are given free access to both compartments, and the time spent in each is recorded. A rewarding drug increases the time spent in the compartment with which it was paired. An increase in time spent in the drug-paired chamber is therefore assumed to reflect approach behavior to addictive reinforcers.

2.2.3. Drug self-administration

Drug self-administration is a powerful tool for ascertaining the reinforcing properties of drugs. A catheter is surgically implanted into the jugular vein of a rat and connected to an injection device (Weeks, 1964). The animal controls delivery of a drug via the catheter by pressing a lever in the operant chamber. The basic premise of this paradigm is that psychotropic drugs can control behavior by acting as positive reinforcers. The number of lever responses is used to assess the reinforcing potential of a drug under various conditions. The characteristics of acquisition, patterning of self-infusions, and profile of extinction (responses after reinforcement is discontinued) of various drugs revealed by this approach provide information about the nature of drug reinforcement and dependence. Using this technique, a high correlation between the reinforcing potency of drugs of abuse in animals and humans has been demonstrated.

2.2.4. Reinstatement model

This experimental model studies relapse to compulsive drug use in animals. Laboratory animals are trained to self-administer

drugs, and then subjected to extinction training during which lever presses are not reinforced with drugs. Reinstatement of extinguished lever responding is determined after non-contingent injections of the drug (De Wit and Stewart, 1981; Stretch et al., 1971), exposure to drug-associated cues (Crombag and Shaham, 2002; Davis and Smith, 1976; Meil and See, 1996), or exposure to stress (Erb et al., 1996; Shaham and Stewart, 1995). During testing for reinstatement, the drug is not available. In a variation of the reinstatement model based on the conditioned place preference paradigm, animals are trained to associate a distinct environment with drug injections. They are then subjected to extinction training during which they are exposed to the same environment in the absence of the drug. Resumption of preference for that environment is then determined after non-contingent priming injections of the drug (Mueller and Stewart, 2000; Parker and Mcdonald, 2000) or exposure to stress (Sanchez and Sorg, 2001). The reinstatement and extinction procedures, which are regarded as valid animal models, are often used to investigate the neuronal substrates underlying drug-seeking behavior (Shaham et al., 2003; Shaham and Hope, 2005; Weiss, 2005). This model has also revealed brain sites and circuits involved in relapse to drug usage (Bossert et al., 2005; Shalev et al., 2002).

2.2.5. Mice with mutated opioid receptors

Null mutant mice models are currently available for assessing the involvement of the opioid system in the behavioral effects of drugs of abuse and are complementary of pharmacological approaches. These mice are mutant for one or all of the three opioid receptor genes, which include the μ-, δ- and κ-opioid receptor, and for opioid peptide precursors which include proopiomelanocortin, preproenkephalin and prodynorphin (reviewed in Fattore et al., 2004; Gaveriaux-Ruff and Kieffer, 2002; Gerrits et al., 2003; Kieffer and Gaveriaux-Ruff, 2002). Opioid agonists or antagonists have been applied in various pharmacological experiments during the past three decades. However, the interpretation of these studies is limited due to non-selective interactions between opioids and opioid receptors *in vivo* (Akil et al., 1984). Comparing mice lacking specific receptors with mice lacking specific opioid peptides may clarify this issue and reveal opioid functions that have been poorly explored by pharmacological methods (Gaveriaux-Ruff and Kieffer, 2002).

3. Cocaine addiction

3.1. Historical perspective

Cocaine is an alkaloid present in the leaves of the shrub *Erythroxylon coca*, which is endogenous to the Andes Mountains in South America. Probably as early as 5000 years ago, the inhabitants of these regions used cocaine by chewing leaves of the shrub (Van Dyke and Byck, 1982). Since the Incas believed coca to be a gift of the Sun God, they initially restricted its use to ceremonial and religious occasions. In Europe, coca chewing never became popular, possibly because the cocaine in the leaves degraded during the long sea voyage. However, once Niemann isolated and characterized the pure alkaloid in 1859, cocaine became popular in both Europe and the United States (Das and Laddu, 1993; Musto, 1991). From the 1920s to the 1960s, cocaine use continued primarily among a relatively small group of "avant garde" artists, musicians and entertainers (Petersen, 1977). Since the 1970s, cocaine use in the United States increased dramatically due to snorting or intravenous injection of the drug, and most recently by smoking of "crack". Crack is the base form of cocaine and comes in a rock crystal that can be heated and its vapors smoked. The term "crack" refers to the crackling sound heard when it is heated. Because crack is smoked, the user experiences a high in less than 10 s. This rather immediate and euphoric effect is one of the reasons that crack became enormously popular in the mid 1980s (National Institute on Drug Abuse, 1999). The effects of crack are similar to those of cocaine, although since crack is smoked additional risks exist including respiratory problems, such as shortness of breath, chest pains, lung trauma and bleeding.

3.2. Effects of cocaine on behavior and physiology

Cocaine usage results in a spectrum of sympathomimetic effects, probably due to blocking of norepinephrine reuptake at peripheral sympathetic neuro-effector junctions. Cocaine-induced catecholamine release causes a pressor response (increased blood pressure) via α_1-adrenergic receptor-mediated vasoconstriction (Branch and Knuepfer, 1992). These neurochemical events cause various physiological effects, including exhilaration, euphoria, a sense of well-being, and self-confidence. Intravenous injection or smoking of cocaine produces a brief "rush", which is sometimes described as like an intense orgasm. At low and moderate doses, cocaine often increases energy, sociability, talkativeness and sexual interest (Grinspoon and Bakalar, 1985; Spotts and Shontz, 1980). However, cocaine can elicit aggressiveness (Licata et al., 1993), which may account for street violence associated with cocaine. In individuals, especially those with prolonged chronic intake, cocaine can cause irritability, anxiety, fear, extreme energy or exhaustion, insomnia, compulsion, incoherent speech, decreased sexual interest, anorexia, and delusions of grandiosity. Most "positive" effects of cocaine, which probably contribute to its powerful reinforcing properties, become "negative" or aversive with increased doses or long use. With regard to brain activity and metabolism, low acute doses of cocaine preferentially stimulate glucose utilization in the nucleus accumbens and medial prefrontal cortex (Porrino et al., 1988). At higher doses, cocaine produces more widespread increases in cerebral glucose utilization and blood flow (Breiter and Helger, 1977). Additionally, at high concentrations cocaine blocks voltage-gated Na^+ channels (Matthews and Collins, 1983). This blocking of axonal Na^+ channels accounts for cocaine's potency as a local anesthetic.

As for the different animal models, behavioral and physiological responses to cocaine depend on various parameters. In the self-administration model, animals readily learn to self-administer cocaine. Although most cocaine self-administration studies involve intravenous administration, smoking of cocaine-base can be achieved in rhesus monkeys (Krattiger et al., 1990). A recent study suggests that cocaine self-administration increases at various doses with prolonged access and that an increase in the rate of responding is positively and inversely associated with session duration and unit dose, respectively. The findings also imply that cocaine intake reaches a ceiling faster at high doses even under short session duration. Therefore, high doses or prolonged access to cocaine are more likely to result in a pattern of cocaine intake that reflects compulsive use (Wee et al., 2007). In a high percentage of animal subjects, unlimited access (23 h daily) to cocaine results in weight loss, convulsions, and eventually death (Johanson et al., 1976). Cocaine sensitizes intracranial self-stimulation in both the medial forebrain bundle (Wise and Hoffman, 1992) and the prefrontal cortex (McGregor et al., 1992). Following a single exposure to cocaine in this model, stimulus frequency-response rate curves retain the same basic shape, but are shifted to the left. This effect, which is reminiscent of shifts in drug dose–response curves, indicates that cocaine enhances the reinforcing effect of the electrical stimulus, and suggests that the psychostimulating effect of cocaine may operate via the same mechanisms that underlie intracranial self-stimula-

tion. The strength of cocaine-induced conditioned place preference behavior depends on the dose, route of administration, and other experimental variables. Typically, the strongest preference for the compartment associated with cocaine is produced by intravenous injections, while intraperitoneal administration is not as strong (Nomikos and Spyraki, 1988).

3.3. Cocaine's mechanism of action via the dopaminergic system

Previously thought to be a neurotransmitter involved only in reward, dopamine is now known to be implicated in driving motivation, predicting reward or failure to receive it, signaling saliency of events (including rewarding, aversive, novel and unexpected stimuli), and facilitating memory consolidation of salient events (Mizuo et al., 1992).

Although many drugs of abuse, including alcohol, amphetamine, cannabis, nicotine, and cocaine, have different primary molecular targets, they all increase dopamine transmission in the nucleus accumbens, mostly in its shell sub-region (Bassareo and Di Chiara, 1997; Di Chiara and Imperato, 1988; Pettit and Justice, 1989; Weiss et al., 1992a). This commonality of action suggests that the mesolimbic dopaminergic system, which projects from the ventral tegmental area to the nucleus accumbens, olfactory tubercule, frontal cortex and amygdale, is involved in the general reinforcing effects of drugs (Koob, 2000; Nimityongskul et al., 1992). With some drugs, such as nicotine, the increase in dopamine is secondary to direct stimulation of dopaminergic cell firing. With other drugs, such as opiates and alcohol, the increase in dopamine is due to reversal of inhibition of dopaminergic cells (Kalivas et al., 1990).

Cocaine acutely affects dopamine neurotransmission as a primary target in the brain. The neurochemical effect of cocaine is achieved by binding to the plasma membrane transporters for dopamine, norepinephrine and serotonin, thereby blocking cellular uptake of these monoamines. Cocaine interacts with all three monoamine uptake systems although with dissimilar potency (Harris and Baldessarini, 1973; Taylor and Ho, 1978). Microdialysis studies further demonstrated that acute cocaine exposure causes increases in extracellular dopamine levels (Carboni et al., 1989; Nomikos et al., 1990), and that the kinetics of such increases correlates with changes in extracellular cocaine concentrations (Hurd et al., 1988; Nicolaysen et al., 1988). Thus, by blocking dopamine transporters, cocaine generates supraphysiological levels of dopamine in the synapse. The dopaminergic receptors D1, D2 and D3 are also associated with the reinforcing properties of cocaine, specifically in the nucleus accumbens shell, the bed nucleus of the stria terminalis, and the central nucleus of the amygdale (Bergman et al., 1990; Caine et al., 1995; Epping-Jordan et al., 1998; Woolverton and Virus, 1989). Selective destruction of the mesocorticolimbic dopamine system using the neurotoxin 6-hydroxydopamine (6-OHDA) resulted in a prolonged decrease in responses to the cocaine self-administration paradigm (Roberts et al., 1980). In addition, self-administration of cocaine is blocked when low doses of dopamine receptor antagonists are systemically injected into rats (De Wit and Wise, 1977; Woolverton and Johnson, 1992). Furthermore, motivational/drive circuits which indicate reward circuits (since pleasure motivates behavior), are governed in part by dopamine, via regulation of higher cortical areas, such as the orbital prefrontal cortex and the anterior cingulate gyrus. Indeed, activity of the orbitofrontal cortex and the anterior cingulate gyrus (Hollerman and Schultz, 1998; Koob, 1996) is down-regulated in cocaine addicts, and is associated with the availability of dopamine D2 receptors (Fowler et al., 2001; Volkow et al., 1993). The disruptions in these regions have been

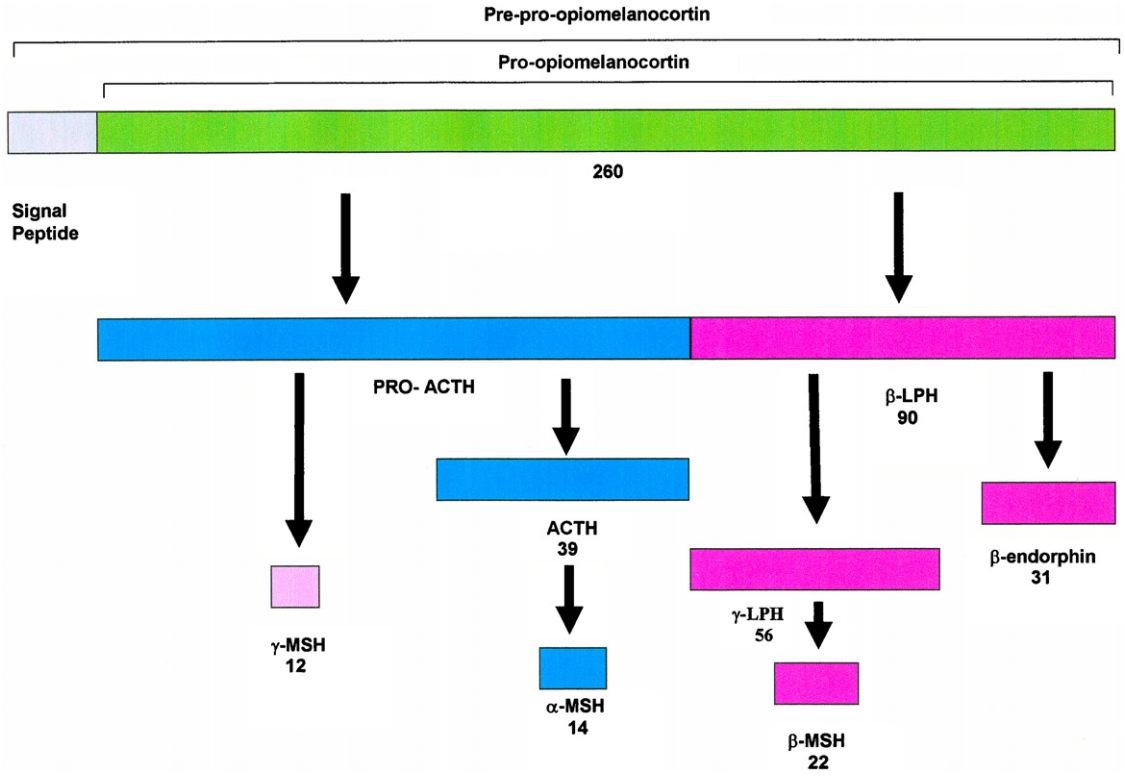

Fig. 2. The opioid precursor proopiomelanocortin and its cleavage products. The gene that codes for the precursor proopiomelanocortin (POMC) is transcribed into mRNA which is then translated to a prohormone of 241 amino acids. Post-translational processing of the large precursor peptide produces several smaller opioid peptides, including β-lipotropin, β-endorphin and non-opioid peptides, such as adrenocorticotropic hormone and α-, β- and γ-melanocyte-stimulating hormone (indicated below each peptide are the number of amino acids in humans).

suggested to cause compulsive drug intake and loss of control by addicted subjects when exposed to the drug or drug-related stimuli (Volkow et al., 2004b).

Acute withdrawal from drugs of abuse is accompanied by a decrease in reward function, as seen by the increase of reward thresholds during intracranial self-stimulation in rats (Markou and Koob, 1991, 1992). The cause of this behavioral phenomenon may be due to hypofunctioning of neurotransmitters involved in the rewarding effect of drugs of abuse, as indicated by decreased dopamine neurotransmission in the nucleus accumbens during cocaine withdrawal (Weiss et al., 1992b). Dopamine has also been implicated in cocaine abstinence in humans (Pilla et al., 1999; Spanagel and Weiss, 1999), and may contribute to the long-lasting vulnerability of former addicts to the drug. Brain imaging studies with human subjects have furthered understanding of dopaminergic neurotransmission in addiction, especially subjective behavioral effects of the drug, such as craving, compulsion and relapse (Volkow et al., 2004a). In these studies, D2 receptor availability in the striatum was lower in drug users than control subjects. This reduction of striatal D2 receptors was prolonged and even persisted after protracted detoxification.

Preclinical studies show involvement of the mesocorticolimbic dopamine system in cocaine-induced reinstatement (Shalev et al., 2002). Cocaine priming-induced reinstatement is mimicked by systemic injections of amphetamine, a dopamine reuptake blocker and dopamine releaser, and D2-like receptor agonists (de Vries et al., 1999; De Wit and Stewart, 1981; Schenk and Partridge, 1999; Self et al., 1996; Wise et al., 1990). However, mixed dopamine agonists and direct D1-like agonists do not mimic the effect of cocaine priming on reinstatement (de Vries et al., 1999; Self et al., 1996; Sinclair et al., 1979). Further pharmacological data indicates differences in the central role of dopamine in different reinstatement models. Injection of SCH-23390, a D1-like receptor antagonist, into several sub-regions of the amygdale attenuates cocaine cue-induced reinstatement (Alleweireldt et al., 2005; See et al., 2001). Furthermore, stress-induced reinstatement of cocaine seeking is attenuated by reversible tetrodotoxin inactivation of the prelimbicortex of the orbitofrontal cortex, an effect mimicked by injections of a D1-like, but not a D2-like, receptor antagonist (Capriles et al., 2003). Thus, D1-receptors in the dorsal prefrontal cortex appear to be involved in cue- and stress-induced reinstatement, while D2 receptors are likely to be involved in cocaine priming-induced reinstatement.

4. The opioid system

4.1. Opioid peptides and their enzymatic generation

Brain extracts displaying opioid-like activity (analgesia) were the first evidence for the existence of endogenous opioids (Kosterlitz and Waterfield, 1975; Terenius and Wahlstro, 1974). Later, researchers isolated and characterized the enkephalins (Hughes et al., 1975) and the C-fragment of the pituitary hormone β-lipotrophin (β-LPH), later referred to as β-endorphin (Bradbury et al., 1976). Several physiological and behavioral effects of enkephalins and β-endorphin, such as rewarding sensations and addictive properties, are similar to those displayed by morphine (Belluzzi and Stein, 1977; Goeders et al., 1984; van Ree et al., 1979). Discovery of another class of endogenous opioids, the dynorphins (Goldstein et al., 1979, 1981), led to the revelation that most endogenous opioids are enzymatically generated from three precursor proteins, prodynorphin (PDYN; Kakidani et al., 1982), proopiomelanocortin (POMC; Nakanishi et al., 1979) and proenkephalin (PENK; Comb et al., 1982). Each of these precursors undergoes processing by proteolitic enzymes, which are stored in the Golgi apparatus along with the precursor. The resulting prohormone peptides are stored in vesicles, where further processing occurs. Depending upon the enzymes present, complex cell-specific patterns of prohormone expression are generated. Post-translational processing of POMC produces several opioid peptides, including β-LPH and β-endorphin (Akil et al., 1988). The POMC precursor also contains biologically active, non-opioid peptides, such as adrenocorticotropic hormone (ACTH), α-, β-, and γ-melanocyte-stimulating hormone (MSH) (see Fig. 2).

4.2. Opioid receptors and motivational tasks

The existence of multiple types of opioid receptors was postulated based on classic dose response curves and agonist–antagonist interactions (Martin et al., 1976). These receptors belong to the family of G protein-coupled receptors have been have been isolated and characterized using molecular and pharmacological techniques (Evans et al., 1992; Kieffer et al., 1992; Knapp et al., 1995; Reisine and Bell, 1993; Uhl et al., 1994). The researchers distinguished between the mu (μ) opioid type receptor which is stimulated by morphine, the kappa (κ) type which binds ketocyclazocine, and the sigma (σ) type which has a high affinity for the experimental compound SKF-10,047 (Martin et al., 1976). Later, a fourth type of opioid receptor, named delta (δ), was identified and named for vas deferens (Lord et al., 1977). Additional research revealed that the σ-type receptor is a non-opioid, thus the main types of opioid receptors are μ, δ, and κ (Manallack et al., 1986).

Endogenous opioid ligands exhibit different preferences for each receptor. β-Endorphin binds with a higher affinity to μ than δ or κ-opioid receptors, naturally indicating that it is the endogenous ligand for this opioid receptor type (Khachaturian et al., 1993; Simon et al., 1973). The affinity of enkephalins for δ-opioid receptors is ~20-fold greater than that for μ-opioid receptors, and dynorphin is presumed to be the endogenous ligand for κ-receptors (Chavkin et al., 1982; Simon, 1991). Of the other novel endogenous opioids isolated, orphanin FQ appears to be an endogenous ligand for ORL-1 (orphan opioid receptor, which has a high degree of homology with the opioid receptors), and endomorphin-1 and -2 are probably highly specific endogenous ligands for the μ-opioid receptor (Meunier et al., 1995; Reinscheid et al., 1995; Zadina et al., 1997).

Opioids with high affinity for μ- and δ-receptors are readily self-administered (using intracranial ventricular administration), whereas ligands for κ-receptors are not. Using the conditioned place preference paradigm, a discriminative effect of opioid receptors was demonstrated. Activation of μ- and δ-opioid receptors results in a dose-related preference for the drug-associated place, while selective κ-agonists cause place aversion (Mucha and Herz, 1985). Place preference occurs following administration of β-endorphin and DPDPE (a specific μ-agonist), and place aversion occurs following administration of E-2078 (a dynorphin derivate). Therefore, reinforcement may result from the activation of either μ- or δ-receptors, and aversion from activation of κ-receptors (Herz, 1997). Naloxone, a non-specific opioid receptor antagonist and CTOP, a selective μ-receptor antagonist, also induce place aversion (Mucha and Iversen, 1984). This implies for a putative endogenous tonic opioid regulation of the reward system, mediated by μ-receptors. Disruption of this regulation results in aversion (for review see Shippenberg et al., 1992). Of the endogenous opioids, β-endorphin is the preferred ligand for μ- and δ-receptors, and thus is a possible candidate for regulating and/or mediating drug-induced reward and reinforcement.

4.3. The opioid system and cocaine

4.3.1. Involvement of opioids in cocaine-seeking behavior

4.3.1.1. Pharmacological approach. Involvement of opioids, such as β-endorphin, in the reinforcing and dependence-creating properties of cocaine has been shown indirectly in pharmacological studies. Most of these studies focused on the relation between opioid receptors and cocaine-seeking behavior. Much evidence exist demonstrating alterations in cocaine-seeking behavior upon blockade of μ- and δ-opioid receptors, which are favored by β-endorphin, hence indirectly indicating that this endogenous opioid is involved in certain aspects of cocaine addiction.

Low doses of the non-specific opioid antagonists naloxone and naltrexone or the specific μ-antagonist CTAP are sufficient to inhibit cocaine-induced conditioned place preference (Gerrits et al., 1995; Kim et al., 1997; Kuzmin et al., 1997; Montoya et al., 2004; Rademacher and Steinpreis, 2002; Suzuki et al., 1992). Administration of the pure μ-opioid antagonist quadazocine, to rhesus monkeys did not alter their cocaine-reinforced responses in the self-administration paradigm (Winger et al., 1992). Assessment of the role of opioid receptors using the self-administration paradigm in rats has also yielded somewhat contradicting results. Injection of naltrexone to the ventral tegmental area, but not to the nucleus accumbens, caudate putamen, central amygdala or medial prefrontal cortex, attenuated acquisition of cocaine self-administration of rats (Ramsey et al., 1999). However, in other studies a decrease (De Vry et al., 1989), an increase (Carroll et al., 1986) or no change (Ettenberg et al., 1982) in cocaine self-administration occurred following systemic pretreatment with naltrexone. Additionally, treatment with naloxone or naltrexone during the maintenance phase causes a decrease in cocaine self-administration in rats (Corrigall and Coen, 1991; De Vry et al., 1989), mice (Kuzmin et al., 1997) and monkeys (Mello et al., 1990). In contrast, naltrexone treatment in the maintenance phase had no effect on cocaine-reinforced responding (Carroll et al., 1986). A possible reason for disparity between the above experiments is the discrete involvement of opioids in the different stages of addiction (i.e. initiation phase compared to maintenance). Most of the studies imply profound involvement of μ-opioid receptors during the maintenance phase, whereas the findings are less consistent as to their role in the initiation phase. The maintenance phase is characterized by a prominent involvement of stress (Goeders, 2002) which may be connected to the effect of opioids, especially β-endorphin, in cocaine rewarding behavior. An additional point that must be taken into account is the different experimental procedures used for the behavioral tasks. In addition to the use of different species duration of drug administration and dosage, the self-administration procedure was preformed differently in the various experiments (using short training sessions of 1 h vs. longer sessions of 3–12 h). High doses or prolonged access to cocaine are more likely to produce a greater effect on receptor regulation than limited exposure (Ben Shahar et al., 2007; Unterwald et al., 2001) and result in a pattern of cocaine intake that reflects compulsive use (Wee et al., 2007). β-Endorphin plasma levels were decreased in obsessive compulsive disorder patients (Weizman et al., 1990) and this finding may imply for an involvement of β-endorphin in compulsive states, including compulsive drug intake. If β-endorphin plays a different role in high/intense cocaine intake (such as in Carroll et al., 1986, using 12-h daily sessions) compared to training for moderate intake, a different seeking pattern of cocaine is expected to develop following naltrexone treatment. Therefore, the finding for the role of naltrexone in cocaine-seeking behavior seems to be ambiguous.

Concerning the role of δ-opioid receptors in mediating cocaine-seeking behavior, it was shown that intracerebroventricular administration of an antisense oligodeoxynucleotide to δ-receptor mRNA inhibited cocaine-induced conditioned place preference in mice (Suzuki et al., 1997). Furthermore, during the maintenance phase of cocaine self-administration, acute blockade of the δ-receptor with naltrindole (a non-specific δ-opioid receptor antagonist) reduced cocaine intake in rats (Reid et al., 1995) and monkeys (Negus et al., 1995), but not in another study with rats in which both self-administration and conditioned place preference paradigms were used (de Vries et al., 1995). Involvement of μ- and δ-opioid receptors in the reinstatement phase of cocaine addiction was rigorously examined in two studies. In one, buprenorphine (a mixed opioid agonist–antagonist), but not naltrexone, caused a dose-dependent suppression of the reinstatement of response by cocaine (Comer et al., 1993). This result indicates that buprenorphine's effectiveness in preventing cocaine priming-induced reinstatement may be related to its opioid agonist action. In the other, more recent study using naltrexone, opioid receptors were shown to be involved in drug-induced (Gerrits et al., 2005) reinstatement of drug-seeking behavior.

So far, there is no consensus in the literature as to the clinical efficacy of opioid antagonists for treatment of cocaine dependence. Chronic treatment of cocaine abusers with the opioid antagonist naltrexone reduced euphoria and "crash" following an i.v. cocaine injection in one study (Kosten et al., 1992), but not in another (Walsh et al., 1996). Several studies have shown the efficacy of buprenorphine, a partial μ-opiate agonist and κ-opiate antagonist in treating concurrent opioid dependence and cocaine abuse. The clinical trials that found buprenorphine treatment to be associated with reductions in cocaine use (Kosten et al., 1989a,b; Montoya et al., 2004; Oliveto et al., 1999; Schottenfeld et al., 1993) used higher buprenorphine doses (8–16 mg daily) than in trials found no evidence of efficacy (Montoya et al., 2004; Oliveto et al., 1993; Schottenfeld et al., 1997; Strain et al., 1994).

In summary, it may be stated that the vast majority of literature indicates that blockade of opioid receptors in the brain decreases both the reinforcing and conditioned motivational effects of cocaine in both animals and humans, depending on a critical dose used and the time of interference.

4.3.1.2. Genetic approaches. The involvement of opioid receptors in drug dependence has been further examined using μ- and δ-opioid receptor knockout mice. μ knockout mice display impaired self-administration and conditioned place preference for morphine, heroin, alcohol, THC, and nicotine (Contet et al., 2004; Kieffer and Gaveriaux-Ruff, 2002). Recently, reduced locomotor activating effects (Chefer et al., 2004), conditioned place preference (Hall et al., 2004), and self-administration (Mathon et al., 2005) of cocaine were shown in μ-opioid receptor knockout mice as well. Another study using a 17-base antisense oligodeoxynucleotide directed against the μ-opioid receptor coding sequence showed that this treatment attenuated cocaine-induced behavioral sensitization and conditioned reward (Hummel et al., 2006). Since different drugs of abuse have different primary loci of action, a prominent and general role of the μ-opioid receptor in the rewarding effects of various substances is indicated.

However, other studies reveal that μ-opioid receptor knockout mice exhibit acute locomotor response to cocaine (Becker et al., 2002; Hall et al., 2004), and demonstrate a sensitized response with repeated cocaine administration (Hall et al., 2004). Additionally, in δ-opioid receptor knockout mice, the locomotor activating effects of cocaine were enhanced (Chefer et al., 2004). Thus, μ- and/or δ-opioid receptors appear to be unessential for acute cocaine-induced locomotor activity and development of

cocaine-induced behavioral sensitization. However, due to limitations of classic knockout strategies (Crawley, 1996; Gerlai, 1996; Lathe, 1996), it is possible that δ-opioid receptors compensated for the loss of μ-opioid receptors, and vice versa. Another possibility is that μ- and/or δ-opioid receptors are involved in cocaine reinforcement, but are not required for cocaine-induced behavioral sensitization, as suggested by studies in which cocaine self-administration was reduced in μ-opioid receptor knockout mice (Mathon et al., 2005). This latter possibility suggests that the opioid system is downstream to the dopaminergic system (see Section 4.4.3 for further detail), and that increased locomotor sensitization cannot be directly interpreted as increased craving or reinforcement. Recently, an attenuation of conditioned place preference, and cocaine-induced motor stimulation, were reported in β-endorphin-deficient mice (Marquez et al., 2008). However, to the best of our knowledge, this is the first study to examine the effect of a β-endorphin knockout on cocaine-seeking behavior.

4.3.2. Imaging of the opioid system upon exposure to cocaine

Advances in imaging technologies, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have facilitated direct investigation of abused drugs' mechanism of action and long-term consequences of addiction in the human brain.

PET can be used to measure radiotracers labeled with short-lived positron-emitting isotopes that selectively bind to specific receptors, transporters, and enzymes involved in the metabolism of neurotransmitters (Volkow et al., 2004a). Using PET, chronic exposure to cocaine in rats increased μ-opioid receptor binding (autoradiography) in discrete brain regions relevant to reward, such as the nucleus accumbens, amygdala, and cingulate cortex (Branch and Knuepfer, 1992; Hammer, 1989; Unterwald et al., 1994; Unterwald, 2001). These findings are supported by studies showing an increase in expression of μ-opioid receptor mRNA in the nucleus accumbens and amygdala, 3 days after exposure to cocaine, or a single day of binge-pattern cocaine administration in rats (Azaryan et al., 1996a,b; Yuferov et al., 1999). Findings inconsistent with the above were seen in only one study: following daily cocaine exposure there was no change in μ-opioid receptor binding in the caudate, and a decrease in binding in the amygdala of guinea pigs (Itzhak, 1993). However, this may be due to species differences, especially the distinctive distribution of various opiate receptors in rat vs. guinea pig (Sharif and Hughes, 1989).

As yet, only a few clinical studies have examined μ-opioid receptor binding in cocaine addicts. PET studies with cocaine addicts demonstrated that μ-opioid receptor binding increases in several brain regions 1–4 days after their last cocaine use. Moreover, μ-opioid receptor binding in the anterior cingulate, frontal and temporal cortex, caudate, and thalamus correlates positively with self-reported cocaine craving (Zubieta et al., 1996). In a more recent study, μ-opioid receptor binding was elevated after 1 day of abstinence in the frontal, anterior cingulate, and lateral temporal cortex, and remained relatively constant for 3 months after abstinence in the anterior cingulate and anterior frontal cortex (Gorelick et al., 2005). In this study, increased binding in several regions correlated positively with cocaine craving and levels of cocaine previously consumed, which further supports a role for μ-opioid receptors in cocaine craving. Cocaine-associated increases in μ-opioid receptor availability may reflect decreased endogenous opioid release or increases in μ-opioid receptor numbers. Furthermore, in animals self-administering cocaine, a decrease in opioid receptor occupancy was seen by autoradiography in restricted subcortical brain regions, including limbic areas (lateral septum, ventral pallidum, nucleus stria terminalis, and amygdala) and several regions of the hypothalamus and thalamus (Gerrits et al., 1999). This decrease in opioid receptor occupancy is probably due to increased release of endogenous opioids in these particular brain regions. These opposite results may suggest that β-endorphin is released during cocaine self-administration (the animal study) and competes with exogenously applied β-endorphin, thus leading to decreased receptor occupancy, while during abstinence (the human study) a marked drop in β-endorphin release will cause an increase in exogenous μ-opioid-ligand binding. Cocaine-induced β-endorphin release in the nucleus accumbens following acute cocaine exposure (Olive et al., 2001; Roth-Deri et al., 2003) supports this possibility.

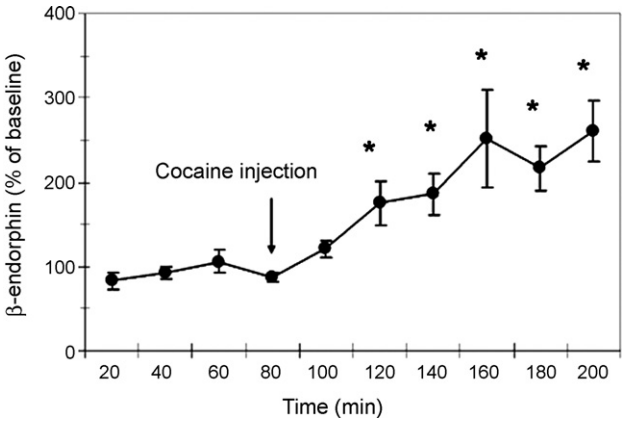

Fig. 3. Effect of acute cocaine on extracellular β-endorphin immunoreactivity levels in the arcuate nucleus. Values are expressed as means ± S.E.M. from five rats/group, $^{*}p < 0.001$ from baseline levels. Extracellular dialysate levels of β-endorphin in the arcuate nucleus significantly increased following cocaine exposure compared to baseline levels and remained elevated 100 min after cocaine injection. Data are from unpublished observations.

Brain function and neurochemistry in addicted subjects has been explored using functional MRI (fMRI), which is based on disruption of magnetic properties in tissue when oxyhemoglobin changes to deoxyhemoglobin (Springer, 1999). Since such a change occurs when brain tissue is stimulated, fMRI is used to measure changes in regional brain activity. Clinical and animal studies have demonstrated alterations in cerebral blood flow in various areas in the brain upon acute cocaine exposure (Breiter et al., 1997; Marota et al., 2000), including areas implicated in the behavioral effects of drugs, such as the nucleus accumbens, ventral tegmentum, caudate, putamen amygdala, and prefrontal cortex. In agreement with these findings, an increase in brain activity in the nucleus accumbens and the arcuate nucleus of the hypothalamus, a main region of endorphinic cell bodies, was found following exposure of rats to cocaine (Roth-Deri et al., 2003). The increased brain activity in the arcuate nucleus was positively correlated with a cocaine-induced increase in extracellular β-endorphin levels in the same region, as measured by microdialysis (Fig. 3). This imaging data, together with neurochemical findings, indicate increased synaptic activity in the arcuate nucleus due to local endorphin secretion following exposure to cocaine.

4.4. The opioid β-endorphin

4.4.1. Synthesis and characterization of β-endorphin

Thirty years ago, the fat-mobilizing pituitary hormone β-lipotrophin (Bradbury et al., 1976) was discovered. Later, its N-terminal fragment (Met-enkephalin) and C-terminal fragment (β-endorphin) were shown to have individual bioactivities. It was found that the enzymatic processing of POMC generates β-lipotrophin, which is cleaved to produce β-endorphin (Nakanishi et al., 1979).

β-Endorphin is an endogenous opioid peptide consisting of 31 amino acids. It is known to be involved in stress, obesity, diabetes, and immune responses (Berczi et al., 1996; Charmandari et al., 2005; Dalayeun et al., 1993). In addition, β-endorphin acts as a neurotransmitter in the central nervous system, and is involved in alcoholism and psychiatric diseases (Bloom et al., 1978; Zakarian and Smyth, 1982). Neurons in the brain that synthesize and release β-endorphin are located mainly in the anterior and neurointermediate lobes of the pituitary gland, the arcuate nucleus of the hypothalamus, and the nucleus tractus solitarius. Neuronal extensions of β-endorphinic cell bodies terminate in heterogeneous brain regions, including the ventral tegmental area and the nucleus accumbens (Finley et al., 1981; Khachaturian et al., 1993), areas involved in reward processes.

In humans, rats, and other species, injection of exogenous β-endorphin into various brain areas or into the cerebrospinal fluid (CSF) exerts an analgesic effect stronger than that of morphine (Bloom et al., 1976; Foley et al., 1979; Loh et al., 1976; Tseng and Wang, 1992). Repeated administration of β-endorphin leads to tolerance to its analgesic action, and to morphine-like withdrawal symptoms upon challenge with naloxone (van Ree et al., 1976; Wei and Loh, 1976). When injected directly into the brain of rats, β-endorphin has rewarding and reinforcing properties (Amalric et al., 1987; Bals-Kubik et al., 1990; Belluzzi and Stein, 1977; Koob, 1992; van Ree et al., 1979), and thus may serve as a neuromodulator in the effects of abused substances.

4.4.2. Interaction of β-endorphin with the dopaminergic system

The study of dopamine-β-endorphin interaction may facilitate understanding of the rewarding and reinforcing potentials of drugs of abuse. Several studies show that activation of the opioid system can alter dopamine release. When μ- and δ-opioid receptor agonists are self-administered in animal models (Devine and Wise, 1994), dopamine release in the nucleus accumbens increases (Devine et al., 1993). This increase occurs via the action of the agonists on GABAergic neurons in the ventral tegmental area, which naturally inhibit dopamine neurotransmission. Ventricular infusions of β-endorphin were shown to increase dopamine release in the nucleus accumbens via μ- and δ-opioid receptors (de Vries and Shippenberg, 2002). This increased dopamine release is likewise due to the inhibitory effect of β-endorphin on GABA-blocking dopaminergic neurons (Di Chiara and North, 1992). Furthermore, β-endorphin-induced reinforcement, as tested by the conditioned place preference paradigm, correlates positively with an increase in dopamine release in the nucleus accumbens (Spanagel et al., 1991). Interestingly, the reinforcing effect of β-endorphin occurs only at doses that stimulate dopamine release, which suggests that β-endorphin is an endogenous mediator of reinforcement, especially for addictive drugs that increase mesolimbic dopaminergic neurotransmission as a secondary target. These findings indicate an opioid–dopamine interaction wherein opioid receptor agonists act at a site upstream from the dopamine synapse in the nucleus accumbens.

However, recent findings suggest a reverse interaction. First, intracranial administration of dopamine into the nucleus accumbens increased local β-endorphin levels (Roth-Deri et al., 2003). Second, the D1 receptor antagonist SCH-23390 and lesioning of the mesolimbic dopaminergic projections blocked cocaine-induced increases in β-endorphin (Fig. 4; Azaryan et al., 1996b; Yuferov et al., 1999) In addition, administration of dopamine receptor agonists in rat increased μ-opioid receptor levels in the striatum and nucleus accumbens, and decreased enkephalin and pre-enkephalin mRNA levels in the striatum (Azaryan et al., 1996a; Chen et al., 1993; George and Kertesz, 1987). Furthermore, several studies show a cocaine-induced increase in μ-opioid receptor expression in the nucleus accumbens and amygdala of rats (Azaryan et al., 1996a) which may be mediated through dopamine receptors, since it was blocked by co-administration of dopamine receptor antagonists (D1- and D2-type; Azaryan et al., 1996a,b). Finally, administration of D2-type dopamine receptor antagonists reduced striatal levels of μ-opioid receptor and increased striatal levels of enkephalin and pre-enkephalin mRNA in rats (Chen et al., 1994; George and Kertesz, 1987; Steiner and Gerfen, 1999). These results suggest that opioid activation is downstream from the dopamine synapse in the nucleus accumbens.

Another known, yet poorly understood dopamine–opioid interaction is the enhanced locomotor response and reward sensitivity to opioid receptor agonists, given systemically or intra-accumbally, following mesolimbic dopamine lesions or chronic treatment with dopamine receptor antagonists (Churchill et al., 1995; Stinus et al., 1992). Our demonstration of a decrease (to ~35% of controls) in β-endorphin basal levels in 6-hydroxydopamine-treated rats may be relevant for the understanding of this dopamine–opioid interaction (Roth-Deri et al., 2003). This result indicates that the basal opioid tone in the nucleus accumbens is under dopaminergic control. Hence, a partial reduction in β-endorphin tone may lead to supersensitivity of opioid receptors in the nucleus accumbens, resulting in an enhanced locomotor response and reward sensitivity to opioid receptor agonists administered to or arriving at the nucleus accumbens. Opioid receptor agonists also induce dopamine-independent behavioral effects in the nucleus accumbens, mediated primarily by μ-receptors (Ikemoto and Panksepp, 1999; McBride et al., 1999; Vaccarino et al., 1985). However, these effects are not involved in the behavioral effects of cocaine (Wise, 1996).

The microdialysis technique has provided additional support for a dopamine–opioid interaction. Dopaminergic function in the arcuate nucleus was eliminated by administering a D2 receptor antagonist via a microdialysis probe. This treatment attenuated the increase in accumbal β-endorphin following cocaine injection (Doron et al., 2006). Moreover, rats chronically exposed to cocaine using the self-administration paradigm displayed extinction-like

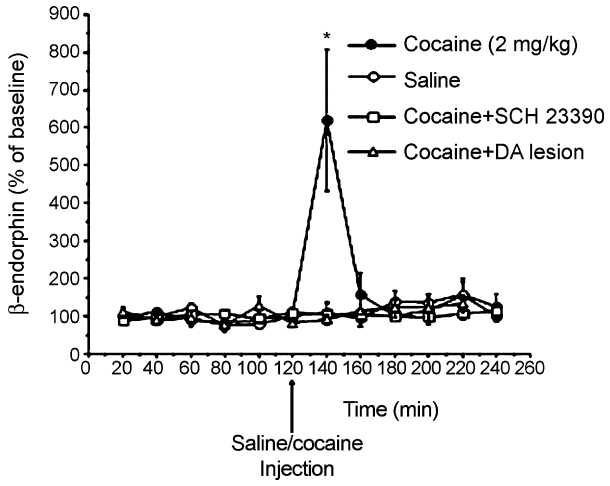

Fig. 4. Effect of dopaminergic lesion or antagonist on cocaine-induced β-endorphin levels in the nucleus accumbens. Dialysates samples were collected at 20 min intervals for 120 min prior to and after cocaine injection (i.v. 2 mg/kg/injection). One group of rats was used to test the effect of SCH-23390 (0.25 mg/kg, i.p., two injections, 20 and 1 min before cocaine injection) on cocaine-induced β-endorphin release in the nucleus accumbens. Another group of rats underwent 6-OHDA dopaminergic lesions 4 weeks before the i.v. and intracranial surgeries, and was tested for the effect of the lesions on cocaine-induced β-endorphin release. The effect of saline or cocaine (2 mg/kg, i.v.) injections on β-endorphin levels is also presented. Values are expressed as means ± S.E.M. from five to six rats/group. $^{*}p < 0.01$ vs. SCH-23390- and 6-OHDA-treated groups. Data are from Roth-Deri et al. (2003).

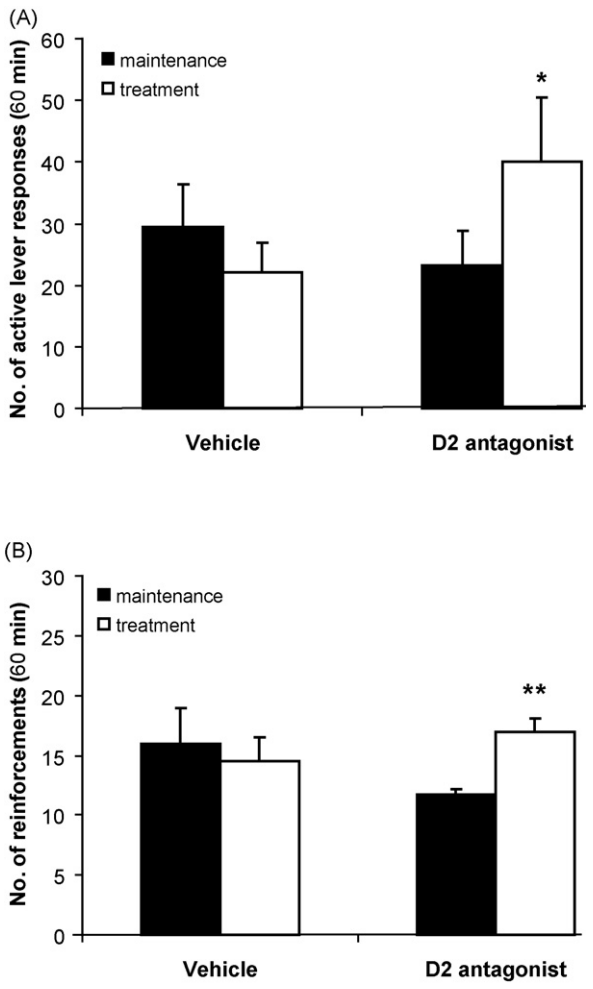

Fig. 5. Cocaine-seeking behavior following injection of a D2-receptor antagonist into the arcuate nucleus. Cocaine-seeking behavior (fixed ratio (FR)-1 schedule, 1 mg/kg/infusion) in rats ($n = 6$) trained to self-administer the drug in operant chambers is measured by the number of presses on the active lever (A) and the number of cocaine infusions consumed by the rats (B). Results are expressed as the mean number of lever presses/infusions ± S.E.M. Significant increases in lever presses ($p < 0.05$) and number of infusions (cocaine consumed; $p < 0.001$) are indicated by an asterisk. The number of non-active lever presses was less than 5 in both groups throughout the entire experiment. Data are from Doron et al. (2006).

behavior, i.e. increased active lever responses and cocaine reinforcements, following blockade of D2 receptors in the arcuate nucleus via microdialysis infusion (Fig. 5; Doron et al., 2006). These findings indicate that dopaminergic function in the arcuate nucleus may regulate the accumbal endorphinic tone and affect the cocaine reward pathway.

Moreover, the levels of endogenous β-endorphin in the anterior part of the limbic system were reduced immediately prior to a scheduled daily session of drug administration, in animals that self-inject heroin or cocaine (Sweep et al., 1988, 1989). At the same time, the basal release of dopamine in the nucleus accumbens decreases (Gerrits et al., 2002). Thus, endogenous opioids in general, and β-endorphin in particular, together with (independently or interactively) mesolimbic dopamine appear to be involved in the mechanism that leads to drug craving and abuse (Gerrits et al., 2003).

4.4.3. Involvement of β-endorphin in cocaine-seeking behavior

In the early 1980s, β-endorphin measurements were performed only in plasma or tissue due to technical limitations.

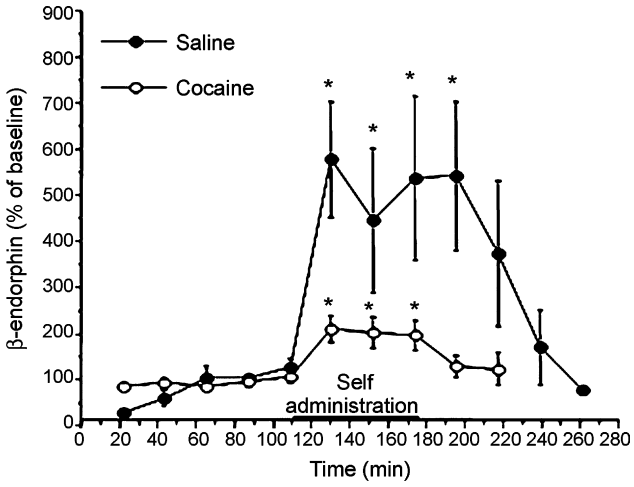

Fig. 6. Effect of cocaine or saline self-administration on extracellular β-endorphin levels in the nucleus accumbens. Dialysate samples were collected at 20 min intervals for 100 min prior to and 40–60 min following cocaine self-administration session. Values are expressed as mean ± S.E.M. from five rats/group. $^{*}p < 0.01$ vs. baseline levels. Extracellular levels of β-endorphin in the nucleus accumbens in the absence of the drug were significantly increased and significantly exceeded the levels obtained following self-administration of cocaine (FR-1 schedule, 1 mg/kg/infusion). Data are from Roth-Deri et al. (2003).

Cocaine-induced β-endorphin release was initially reported independently by two laboratories (Forman and Estilow, 1988; Moldow and Fischman, 1987). Chronic treatment with cocaine increased β-endorphin release *in vitro* from the pituitary (Forman and Estilow, 1988), but not from the hypothalamus (Forman and Estilow, 1988; Harsing et al., 1982). Furthermore, the amounts of β-endorphin immunoreactivity in the anterior part of the limbic system (nucleus accumbens, septum, hippocampus, and rostral striatum) decreased in animals that self-administered cocaine (Sweep et al., 1988, 1989). Based on these findings, it was hypothesized that β-endorphin release increases during cocaine self-administration. Two decades passed before β-endorphin levels were measured extracellularly in various brain regions following exposure to cocaine. More accurate findings obtained with the microdialysis technique confirmed and extended the findings of the studies described above. Both experimenter-delivered and self-administered cocaine transiently elevate extracellular levels of β-endorphin in the nucleus accumbens (Fig. 6; Roth-Deri et al., 2003). Cocaine also increases extracellular levels of β-endorphin in the arcuate nucleus, the main site of endorphinic cell bodies (Fig. 3).

The reinforcing effect of β-endorphin was demonstrated using behavioral experiments. Rats self-administer β-endorphin into the cerebral ventricles (van Ree, 1979) and exhibit dose-dependent place preference for an environment paired with β-endorphin injected intracerebroventricularly (Amalric et al., 1987; Bals-Kubik et al., 1988). The reinforcing dose of β-endorphin also produces an increase in locomotor activity (Spanagel et al., 1991). Pre-treatment with naloxone attenuates the rewarding effect of β-endorphin (Amalric et al., 1987), while CTOP and ICI 174864 (a specific δ-opioid receptor antagonist) abolish this effect (Bals-Kubik et al., 1990). These findings indicate positive reinforcing properties of β-endorphin in the central nervous system, and emphasize the role for β-endorphin in processes underlying cocaine dependence.

4.4.3.1. Cocaine acquisition and β-endorphin. Until recently, it has been impossible to ascertain which endogenous opioid peptides modulate the incentive value of cocaine. Opioid peptides are not highly selective for any opioid receptor subtype, thus the

pharmacological means employed could not supply a definite conclusion. It was recently demonstrated the specific contribution of β-endorphin to the acquisition of cocaine self-administration (Roth-Deri et al., 2006) by partial-specific lesioning, using estradiol valerate (EV), of β-endorphin-producing neurons in the arcuate nucleus of the hypothalamus (see Desjardins et al., 1993). A single pretreatment with EV reduced β-endorphin levels by 50% and abolished cocaine acquisition, as ascertained by low levels of active lever responses and cocaine reinforcements during 12 days of cocaine self-administration. Studies show that pretreatment with EV decreases the plasma levels of estrogen in addition to β-endorphin (Brawer et al., 1980; Desjardins et al., 1990, 1993). Nevertheless, EV-treated rats which received estrogen replacement exhibit low cocaine-seeking behavior, similar to EV-treated rats with low estrogen plasma levels. These results imply that hypothalamic endorphinic neurons, rather than estrogen plasma levels, mediate cocaine reinforcement in these rats. Moreover, after 12 days of self-administration training, EV-treated rats exhibit less active lever presses than controls in a dose–response trial (Roth-Deri et al., 2006). This finding rules out the possibility that EV pretreatment produces a rewarding effect by increasing the sensitivity to cocaine.

Another study shows that β-endorphin knockout mice are less responsive to the stimulating locomotor effects of cocaine, which suggests that β-endorphin is involved in cocaine-induced locomotor activation (Marquez et al., 2008). In the same study, cocaine also produced a lower degree of conditioned place preference in β-endorphin knockout mice, which indicates a reduced rewarding effect. This study directly demonstrates a modulatory role for cerebral β-endorphin in cocaine reinforcement and is in agreement with indirect studies that monitored the effect of endogenous opioids on cocaine acquisition using opioid receptor antagonists (Kuzmin et al., 2000; Ramsey and van Ree, 1991).

4.4.3.2. Cocaine maintenance and β-endorphin. The transition point from controlled drug use to drug abuse is at present not clear. However, involvement of β-endorphin in the maintenance phase may be related to unique characteristics of this transition, including increased involvement of the stress system and craving for the drug. It was shown that self-administered cocaine increases extracellular levels of β-endorphin in the nucleus accumbens during the maintenance phase (Fig. 6, Roth-Deri et al., 2003). Previously, it was shown that tissue levels of β-endorphin in the anterior part of the limbic system decrease just before a scheduled daily self-injection session of cocaine or heroin (Sweep et al., 1988, 1989), which suggests release of β-endorphin to the synapse. Interestingly, both decreased β-endorphin content and increased endogenous opioid release occurred just before a scheduled cocaine self-administration session would have taken place, i.e. when the desire or need for the drug is assumed to be high. These findings indicate involvement of endogenous opioids and β-endorphin in the subjective feelings of addicts that lead to daily drug intake (Gerrits et al., 2003). Although demonstrating that cocaine administration alters endogenous β-endorphin levels, these studies do not address the exclusive role of β-endorphin in the rewarding and reinforcing effects of cocaine. Recent findings demonstrate direct involvement of β-endorphin in these effects. A bilateral injection of anti-β-endorphin antibody to the nucleus accumbens of rats during the maintenance phase of cocaine self-administration significantly increases active lever responses and infusions of cocaine (Roth-Deri et al., 2004). This increase in lever responses is reminiscent of the response of rats to cocaine extinction (Yokel, 1987). Thus, a decrease in the levels of endogenous β-endorphin by anti-β-endorphin antibodies might suppress the rewarding effect of cocaine. Indeed, the shift of the dose–response curve to the right following administration of anti-β-endorphin antibodies suggests that these antibodies antagonize the rewarding and reinforcing effects of cocaine. Therefore, possibly to compensate for decreased stimulation of the reward system, these rats increase the active lever presses to obtain additional cocaine reinforcements, attempting to attain the same subjective sensation of reward to which they had become accustomed during maintenance. However, the anti-β-endorphin antibodies do not appear to completely block the sensitivity of rats to cocaine, since their levels of lever pressing, although high, were only half those of rats in extinction trials (saline substituted for cocaine in the injector). Consistent with these findings, lateral ventricular infusion of anti-β-endorphin antibodies significantly increases lateral hypothalamic intracranial self-stimulation, which indicates involvement of β-endorphin in self-stimulating reward (Carr, 1990; Schaefer, 1988).

4.4.3.3. Cocaine extinction and β-endorphin. The first step of abstinence is extinction of a former drug-consuming habit. Following an extinction trial from cocaine self-administration in rats, an increase is seen in accumbal extracellular β-endorphin, which is greater than that induced by cocaine (Roth-Deri et al., 2003). In agreement with this finding, extinction of self-stimulation behavior (lever pressing) following termination of a non-drug reward (an electrical stimulus) induces a rapid increase in accumbal β-endorphin levels (Zangen and Shalev, 2003). The same effect was observed during extinction from heroin and during exposure to foot shock. Thus, the increases in β-endorphin levels in these studies may be related to a frustration/stressful component induced by reward removal (Amsel, 1962).

4.4.3.4. Opioids and relapse to cocaine usage. Little is known about the involvement of the opioid system in relapse to cocaine usage. In rats, acute administration of naltrexone, an opioid antagonist, does not affect cocaine-induced reinstatement (Comer et al., 1993; Gerrits et al., 2005; Stewart et al., 1984). However, blockade of opioid receptors by repeated treatment with naltrexone reduces cocaine-induced reinstatement of drug-seeking behavior (Gerrits et al., 2005), which suggests a modulating role for opioid receptors in cocaine reinstatement (Tang et al., 2005). Tang et al. (2005) show that cocaine-induced reinstatement requires endogenous stimulation of μ-opioid receptors in the ventral pallidum. This is consistent with findings showing that reinstatement of cocaine-seeking is modulated in part by co-released enkephalin and GABA from the accumbens-ventral pallidal projection, a modulation that may involve inhibition of GABA release by presynaptic μ-receptors (Tang et al., 2005). Buprenorphine reduces cocaine-seeking following cocaine priming and reinstatement, although it does not affect stress-induced reinstatement in rats (Comer et al., 1993; Sorge et al., 2005). Since similar effects occur with etonitazene (a high-efficacy opioid agonist) the effectiveness of bruprenorphine in preventing reinstatement by a priming injection of cocaine is probably related to its opioid agonist activity (Comer et al., 1993). Opioid agonists may affect cocaine-induced reinstatement through their sedative properties, masking the stimulating (motivational) of the drug (Shalev et al., 2002). A specific role for β-endorphin in reinstatement has not yet been shown.

4.4.4. β-Endorphin and other substances of abuse

4.4.4.1. β-Endorphin and ethanol consumption. The demonstration of a decrease in ethanol consumption following exposure to opioid antagonists in rodents and monkeys prompted extensive studies on the relationship of ethanol consumption and the opioid system

(Gianoulakis, 2004; Herz, 1997; Oswald and Wand, 2004; Ulm et al., 1995). Since activation of μ- and δ-opioid receptors correlates with positive reward, and activation of κ-opioid receptors is associated with aversion sensation (Herz and Spanagel, 1995), investigators have focused on enkephalin, and especially β-endorphin, which bind to δ- and μ-opioid receptors, as mediators of the behavioral effects of ethanol.

Results obtained using selective opioid antagonists indicates that both the β-endorphin and enkephalin systems are involved in maintenance of ethanol consumption (Herz, 1997). Naloxone was the first opioid receptor antagonist shown to decrease ethanol consumption in rodents (Froehlich et al., 1990; Hubbell et al., 1986; Marfaing-Jallat et al., 1983; Samson and Doyle, 1985; Weiss et al., 1990). Similar findings were later reported with naltrexone and nalmefene, another non-selective opioid antagonist (Altshuler et al., 1980; Hubbell et al., 1991; Kornet et al., 1991; Myers et al., 1986; Volpicelli et al., 1986). Specific antagonists for δ-opioid receptors, such as naltriben, naltrindole and ICI 174864 also decrease ethanol self-administration in rodents and monkeys (Froehlich et al., 1991; Krishnan-Sarin et al., 1995a,b). However, in ethanol-preferring AA rats, CTOP a μ-opioid receptor antagonist, but not ICI 174864 a δ-opioid receptor antagonist, attenuates ethanol consumption (Hyytia, 1993). Despite these discrepancies, the use of more selective opioid antagonists has helped to establish that both β-endorphin and enkephalin systems are important for the maintenance of ethanol consumption (Oswald and Wand, 2004). A literature search for publications addressing the issue of alcohol use while on methadone (a partial opioid agonist) – maintenance – treatment was conducted. Of 15 heterogeneous clinical studies that met inclusion criteria, 3 studies supported an increase in alcohol use, 3 supported a decrease in alcohol use, and 9 supported no change in alcohol use (Srivastava et al., 2008).

Mice with genetically mutated opioid receptors have yielded conflicting findings. Mice lacking μ-opioid receptors either consumed less alcohol than controls (Hall et al., 2001) or did not self-administer alcohol at all (Roberts et al., 2000). However, alcohol was self-administered by δ-opioid receptor knockout mice (Roberts et al., 2001), possibly due to a compensatory increase in μ-opioid receptor activity in the absence of δ-opioid receptors (Goody et al., 2002).

Both β-endorphin and enkephalin are the primary endogenous ligands for μ-opioid receptors, therefore the relative contribution of each opioid to the mediation of ethanol consumption should be determined. The role of β-endorphin and enkephalin in ethanol consumption was studied using mice completely lacking one or both of these peptides. β-Endorphin knockout mice demonstrated greater ethanol consumption (Grahame et al., 1998, 2000; Grisel et al., 1999; Hayward et al., 2004) under various experimental conditions. Surprisingly, ethanol self-administration in mice genetically lacking β-endorphin and enkephalin was similar to that of wild-type mice (Hayward et al., 2004), suggesting that the rewarding effects of ethanol do not require β-endorphin or enkephalin signaling. Moreover, using mice lacking only enkephalin minimally effected ethanol self-administration (Hayward et al., 2004). The apparent discrepancies between findings in μ-receptor and β-endorphin- and enkephalin-deficient mice may be due to different experimental paradigms and different genetic backgrounds of the mice used, or alternatively, by other endogenous μ-opioid receptor ligands, such as endomorphin, which subserves ethanol reinforcement, and non-opioid pathways which compensate for the loss of β-endorphin and enkephalin (Hayward et al., 2004).

Opioids were additionally found to be involved in ethanol-induced dopamine neurotransmission, which further suggests that they are implicated in the reinforcing properties of this substance. Ethanol-induced dopamine release in the striatum and the nucleus accumbens decreases following systemic or local administration, respectively, of opioid antagonists (Acquas et al., 1993; Benjamin et al., 1993; Widdowson and Holman, 1992). These findings indicate a role for opioid mediation of ethanol effects and accumbal dopaminergic neurotransmission during ethanol exposure (Oswald and Wand, 2004). Opioid function was also seen in the amygdala, another mesolimbic brain region related to addiction (Koob, 1999; Koob and Roberts, 1999; McBride, 2002), following ethanol exposure. Microinjection of an opioid antagonist into the amygdala caused a decrease in ethanol self-administration in trained rats (Heyser et al., 1999), probably because the medial nucleus of the amygdala is rich in μ- and δ-opioid receptors (Mansour et al., 1995).

In humans, involvement of the opioid peptides in ethanol-seeking behavior was examined by measuring endogenous β-endorphin levels in the cerebral spinal fluid (Genazzani et al., 1982) and blood plasma (Aguirre et al., 1990; Inder et al., 1998; Marchesi et al., 1997; Vescovi et al., 1997) of subjects at high risk for alcohol intake. One theory states that humans who differ in their vulnerability to alcoholism would also demonstrate inherited differences in β-endorphin sensitivity to ethanol (Gianoulakis, 1996). This was supported by studies in which subjects with a family history of alcoholism exhibited lower plasma levels of β-endorphin, but a greater release of β-endorphin following exposure to ethanol than low risk subjects (Gianoulakis et al., 1989, 1996). A study with twins further emphasizes that the β-endorphin response to ethanol may indicate high genetic vulnerability for alcoholism (Froehlich et al., 2000).

Recently, the relationship between genetic polymorphism of the endogenous opioid system and vulnerability to alcoholism was examined. One polymorphism in the μ-opioid receptor, which involves an A118G nucleotide exchange, causes an Asn40Asp substitution in the extracellular N-terminal domain of the receptor (Bergen et al., 1997; Wendel and Hoehe, 1998). *In vitro*, the μ-receptor, which is encoded by the 118G allele, binds β-endorphin three times stronger than the common 118A allele. Since the 118G variant is activated more potently following interaction with β-endorphin (Bond et al., 1998), this polymorphism may account for the inherited vulnerability for alcoholism (Bergen et al., 1997; Gelernter et al., 1999; Rommelspacher et al., 2001; Sander et al., 1998; Town et al., 1999). However, studies of genetic association have yielded inconsistent findings with regard to the relationship between the A118G polymorphism and alcoholism (Bergen et al., 1997; Gelernter et al., 1999; Rommelspacher et al., 2001; Sander et al., 1998; Town et al., 1999). Frequencies of the 118A allele and +118A/A genotype were higher in alcoholics than controls in some studies, while other studies have demonstrated no difference between groups. In contrast, the frequency of the Asp40 (118G allele) variant in alcoholics was higher than in control (Rommelspacher et al., 2001). The same study showed similar frequencies of the 118G allele in controls compared to subsets of the alcohol-dependent participants who had a family history of alcoholism, early onset of alcoholism, or severe withdrawal symptoms. One should note that the behavioral phenotype of alcoholism is variable and is likely to be influenced by multiple genes. Each gene contributes a small amount of variance to the phenotype. Under these circumstances, inconsistencies in findings across studies are conceivable (Comings and Blum, 2000).

Two clinical trials were performed in the early 1990s to assess the therapeutic potential of opioid antagonists for alcoholism. In these and other studies (Anton et al., 1999; Chick et al., 2000; Guardia et al., 2002; Morris et al., 2001; O'Malley et al., 1996), treatment of alcoholics with naltrexone for short periods of 12 weeks decreased relapse and the amount of alcohol consumption. However, in another study, both short- and long-term treatment

with naltrexone did not affect relapse to alcohol (Krystal et al., 2001). Recent findings show a reduction in alcohol craving and relaps in heavy drinkers following naltrexone treatment (Pettinati et al., 2006; Tambour and Quertemont, 2007). These conflicting findings may be due to diverse characteristics of the subjects and the psychosocial support administered. Studies show that naltrexone can decrease craving for ethanol in alcoholics for up to 1 year (Heinala et al., 2001; Rubio et al., 2001). The opioid antagonist nalmefene is structurally similar to naltrexone, but with a number of potential pharmacological advantages for the treatment of alcohol dependence, including greater oral bioavailability, longer duration of antagonist action, and more competitive binding with opioid receptor subtypes that are thought to reinforce drinking. Treatment with nalmefene was effective in preventing relapse to heavy drinking in alcohol-dependent outpatients (Mason et al., 1999). These results further indicate a relationship between β-endorphin, ethanol reinforcement and vulnerability to alcoholism.

4.4.4.2. Nicotine and β-endorphin. Nicotine stimulates cholinergic receptors located in the ventral tegmental area and nucleus accumbens, which are important components of the mesolimbic reward pathway. In mice exposed to nicotine, endogenous opioid levels are increased in the nucleus accumbens and striatum (Davenport et al., 1990; Dhatt et al., 1995; Houdi et al., 1991; Pierzchala et al., 1987; Pomerleau and Pomerleau, 1984).

Repeated administration of nicotine induces development and expression of behavioral sensitization in wild-type mice, but not μ-opioid receptor knockout mice (Yoo et al., 2004). Additionally, conditioned place preference for nicotine is reduced in μ-opioid receptor knockout mice (Berrendero et al., 2002). Exposure to an environment associated with the rewarding properties of nicotine causes increased CREB phosphorylation, similar to that seen following nicotine administration, in wild-type but not opioid receptor knockout mice (Walters et al., 2005). Moreover, acute administration of naloxone blocks both molecular (CREB phosphorylation) and behavioral (nicotine reward) responses of wild-type mice in the place preference paradigm (Walters et al., 2005). Since CREB is thought to be centrally involved in the rewarding properties of various drugs of abuse, these results imply involvement of μ-opioid receptors in mediating nicotine reward. This assertion is further supported by pharmacological intervention using glycyl-glutamine, a dipeptide synthesized from β-endorphin, which antagonizes μ receptors. Administration of this peptide caused inhibition of the acquisition and expression of nicotine conditioned place preference (Goktalay et al., 2006).

Whereas acute exposure of rats to cocaine, amphetamine and alcohol increases β-endorphin in the nucleus accumbens, acute exposure to nicotine does not (Olive et al., 2003). Moreover, in the mediobasohypothalamus of rats, mRNA for POMC decreases following long-term nicotine administration, a decrease that persists for 21 days after withdrawal (Rasmussen, 1998). In another study, nicotine exposure caused no change in β-endorphin plasma levels (Wewers et al., 1994).

In humans, naltrexone significantly lowers the relative reinforcing value of nicotine in a cigarette choice paradigm (Rukstalis et al., 2005). Furthermore, levels of β-endorphin were elevated in most clinical studies that examined the correlation between β-endorphin and nicotine exposure (Backon, 1989; Gilbert et al., 1992; Meliska and Gilbert, 1991; Seyler et al., 1986). Interestingly, plasma levels of β-endorphin in light, but not heavy smokers were reported to be significantly higher than in non-smokers (del Arbol et al., 2000). The authors hypothesized that this could be due to nicotine-induced blockade of cholinergic receptors that caused elevated dopamine levels (Sastry, 1995), which were shown to abrogate β-endorphin production in one study (Myers, 1996). However, this is inconsistent with several studies showing dopamine-stimulated β-endorphin release (Alfoldi et al., 1991; Farah and Mueller, 1989; Roth-Deri et al., 2003). In another study, nicotine exposure caused no change in β-endorphin plasma levels (Wewers et al., 1994).

4.4.4.3. Tetrahydrocanabinol (THC) and β-endorphin. Cannabinoids, like opioids, induce antinociception, reward, and dependence (Felder and Glass, 1998). Interactions between cannabinoids and the opioid system have been implicated in pharmacological studies (Manzanares et al., 1999). Furthermore, acute responses to THC, the psychoactive component in marijuana, including analgesia, hypothermia and hypolocomotion, were not altered in μ- and κ-knockout mice, whereas THC reward, as measured by conditioned place preference paradigm, was abolished (Ghozland et al., 2002).

Information concerning the interaction between THC and β-endorphin is limited. Exposure to THC elevates β-endorphin-like immunoreactivity in plasma and discrete brain regions (Kumar et al., 1984; Patel et al., 1985). In addition, neonatal exposure to THC elevates β-endorphin levels in various brain regions of adult male rats (Kumar et al., 1990). In a THC self-administration paradigm, β-endorphin release was increased in the nucleus accumbens and ventral tegmental area (Solinas et al., 2004). The same study shows that systemic morphine and local tegmental, but not accumbal, β-endorphin potentiate discrimination of THC, demonstrated using a two-lever choice THC-discrimination procedure. Additionally, the opioid antagonist naloxone reduced the discriminative effects of THC.

4.4.4.4. β-Endorphin and memory. A process of learning and memory was suggested, to explain the shift in drug intake to a habitual stage (Kelley, 2004; Lee et al., 2006). Involvement of β-endorphin in post-operative memory in the amygdala was suggested (Introini-Collison et al., 1995; McGaugh et al., 1993). Additionally, retrieval of avoidance learning is modulated by β-endorphin and enhanced by naloxone (Barros et al., 2003; Quevedo et al., 1997). In humans, opioid receptor blockade, using a single oral dose of naltrexone, may specifically improve incidental recognition memory following physiological arousal (Katzen-Perez et al., 2001). These findings demonstrate that opioid peptides in general and β-endorphin in particular, mediate alterations in specific aspects of human memory during heightened emotional states. This may explain why memories can be selectively modified under stressful events, such as those experienced by addicts (Katzen-Perez et al., 2001). For example, activation of β-endorphin in the nucleus accumbens may be involved in appetitive motivational processes underlying drug-seeking behavior which are controlled by exposure to the drug-memorized cues. Both the amygdala and the NAc have been shown to be involved in conditioned learning (Brown et al., 1992). Volkow et al. and others (Di Chiara, 1999; Meil and See, 1996; Volkow et al., 2002) postulate that the activation of the hippocampus and amygdala in association with a drug-related context would activate the orbitofrontal cortex and anterior cingulate gyrus in expectation of the reinforcer, which in turn would activate DA cells via fronto-mesencephalic connections (Karreman and Moghaddam, 1996a,b). This would lead to a further increase in the salience of the drug and resultant craving. The drug-induced increases in DA levels and will further strengthen the memory and the motivational value of the drug (Volkow et al., 2002). This increase in DA levels triggers β-endorphin release in areas innervated by the ArN, e.g. the NAc and perhaps in the amygdala. Additionally, both dopaminergic and μ receptors are found in the amygdala (Jacobsen et al., 2006), which further supports a role for β-endorphin in learning and memory pertaining to the addiction process.

5. Concluding remarks and perspectives

Involvement of β-endorphin in drug-induced reward and reinforcement is supported by evidence reviewed herein from studies performed during acquisition, maintenance and withdrawal stages of addictive drug usage, i.e. cocaine, alcohol, nicotine and THC. Whether endorphins are also involved in drug reinstatement has yet to be determined.

We speculate that the reward pathways for different addictive drugs converge to a common pathway in which β-endorphin is a modulating element. As such, the observed elevations in brain levels of β-endorphin during drug self-administration and extinction of the drug-reinforced behavior would be functionally significant. For example, β-endorphin in the nucleus accumbens may activate appetitive rewarding. This possibility is supported by opioid receptor blocker-mediated reduction of the conditioned reinforcing effects of addictive drugs.

The interaction between β-endorphin and dopamine in the brain yields bi-directional effects. Accumbal dopamine stimulates β-endorphin release and vice versa (Di Chiara and Imperato, 1988; Roth-Deri et al., 2003; Spanagel et al., 1990a,b), suggesting that the neuronal effects of β-endorphin can occur both downstream and upstream to the dopaminergic synapse. This would result in an uncontrollable dopamine-β-endorphin circuit activation, unless balanced via another factor. Binding of excessive β-endorphin, generated by addictive drugs, to low-affinity κ-opioid receptors in the nucleus accumbens, may cause a decrease in dopamine levels and thus in the rewarding power of the drug (Herz, 1998; Spanagel et al., 1990b). Moreover, control of this circuit may be achieved at endorphinic cell bodies within the arcuate nucleus via μ-opioid and GABA-B receptors (Loose et al., 1991) or via the dopaminergic tone of the arcuate nucleus, which regulates accumbal endorphinic neurotransmission, and hence affects the cocaine reward pathway (Doron et al., 2006). Alternatively, the accumbal dopamine-β-endorphin circuit may be driven (or reset) from distinct brain regions that innervate both the nucleus accumbens and the arcuate nucleus, such as the amygdala (Haines and Ard, 1997). Retrograde staining of the arcuate nucleus region with fluorogold implied innervation of this region by the amygdala (unpublished data), which supports this possibility. The amygdala, which is a component of the mesolimbic dopamine system, is involved in cocaine-seeking and craving induced by drug-associated cues (Bonson et al., 2002) and in incubation of cocaine craving (Lu et al., 2007). Furthermore, neuroadaptations of glutamate receptors (Lu et al., 2005) and increased levels of the plasticity-related growth factor BDNF (Grimm et al., 2003) are seen in the amygdala upon withdrawal from cocaine self-administration. Increased activity of the amygdala is associated with long-term increases in craving and compulsivity following massive exposure to an addictive drug (Fuchs et al., 2006; Goto and Grace, 2005; Kalivas and Volkow, 2005; Lu et al., 2007). Therefore, increased input of the amygdala to the arcuate nucleus may induce the observed increases in accumbal β-endorphin during exposure to the drug (see Fig. 7).

β-Endorphin has interesting effects on post-operative memory and retrieval of avoidance (Quevedo et al., 1997). In humans, opioid receptor blockade improves incidental recognition memory following physiological arousal, indicating its role in memory during heightened emotional states (Katzen-Perez et al., 2001). This may explain why memories can be selectively modified under stressful events, such as those experienced by addicts.

Cocaine can induce anxiogenic (stress-like) responses, since it also potently activates the hypothalamic–pituitary stress axis (Sarnyai, 1998; Sarnyai et al., 2001). Moreover, exposure to different stressors (e.g. tail pinch, fox odor, and foot shock in rats) activates endorphinic neurotransmission (Marinelli et al., 2004; Zangen and Shalev, 2003). Based on the effect of stress on cocaine self-administration (Piazza and Le Moal, 1998) and reinstatement (Shaham et al., 2000), it can be reasoned that elevations in accumbal β-endorphin during extinction mediate stress-induced cocaine-seeking. However, this possibility is unlikely, since the opioid receptor antagonist, naltrexone, has no effect on stress-induced relapse to drug usage (Le and Shaham, 2002; Shalev et al., 2002). Nonetheless, β-endorphin may contradict unpredictable distress (Goeders and Guerin, 1994; Self and Choi, 2004), which could account for the tremendous increase in β-endorphin release on the first day of extinction following maintenance (Roth-Deri et al., 2003; Zangen and Shalev, 2003). Moreover, increased cocaine-seeking behavior occurs following transient elimination of accumbal β-endorphin in rats trained to self-administer cocaine (Roth-Deri et al., 2004). This further implies a discrete role, beyond that of mediating the cocaine reward pathway, for β-endorphin in mitigating the stress response.

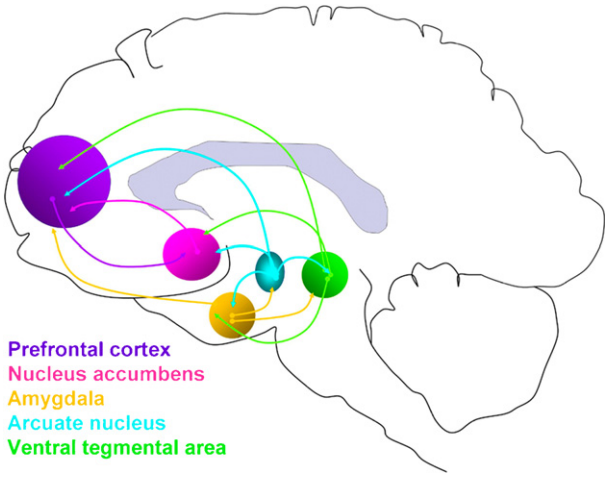

Fig. 7. Diagram showing the possible interactions between the main origin of the endorphinic cell bodies (arcuate nucleus of the hypothalamus [ArN]) and the brain nuclei responsible for the reinforcing effects of addictive drugs. Endorphinic neurons in the arcuate nucleus send projections to brain regions of the limbic system, including the VTA, nucleus accumbens, frontal cortex, septum, hippocampus and amygdale (Khachaturian, 1985). A bi-directional relationship exists whereby the amygdala innervates the ArN, thus implicating the ArN in drug-related memory processes and heightened emotional states caused by drug exposure. In addition, the regions innervated by the VTA are depicted. *Note*: An overlap exists between areas innervated by the ArN and the VTA (Fuxe et al., 1985), implying for a possible interaction between endorphinic and dopaminergic systems (see Section 4.4.2).

Although drugs of abuse have different acute mechanisms of action, their brain pathways of reward exhibit common functional effects upon both acute and chronic administration (Nestler, 2005). Herein, evidence for involvement of β-endorphin in a common mechanism underlying the behavioral effects of substances of abuse was reviewed. Currently, evidence supports a prominent role for β-endorphin in the reward pathways of cocaine and alcohol. The existing information indicating the importance of β-endorphin neurotransmission in mediating the reward pathways of nicotine and THC, is thus far circumstantial. Therefore, behavioral assessments following elimination or augmentation of cerebral β-endorphin are necessary to determine its definite role.

Understanding the role of β-endorphin in mediating the addictive properties of non-opioid drugs of abuse may assist in providing potential therapeutic strategies for the prevention of relapse to drug addiction. Such treatments may be more efficient

compared to general opioid-targeted treatments currently available in the clinic.

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