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Opioids, Reward and Addiction: An Encounter of Biology, Psychology, and Medicine

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I. Introduction

If the entire materia medica at our disposal were limited to the choice and use of only one drug, I am sure that a great many, if not the majority, of us would choose opium (Macht, 1915).

A. Early History

Opium is the dried milky juice of the unripe seed capsule of the poppy, the *Papaver somniferum*. The word opium is derived from "opos", the Greek word for juice. The first reference to this juice was by Theophrastus (300 B.C.), mentioning it mekonion. The medicinal and nonmedicinal use of opium by the ancient Greeks and Romans is not well documented, but it is generally believed that they were aware of the euphoric and narcotic (from the Greek word for stupor) properties of opium. They probably also knew that it could be applied for pain relief and dysentery. There are suggestions that the opium poppy was cultivated in Persia back to the end of the third millennium B.C. Arabic physicians used opium quite often and Arabic traders brought opium from the eight century A.D. on, first to the East, to India and China, and later to Europe. The Mohammedan prohibition of wine and the banning of tobacco smoking in China may have favored the spread of opium. With the "worldwide" availability of opium, the phenomenon addiction raised its head. An attempt to forbid the import of opium into China by the authorities, led to the so-called "Opium War" between England and China, with the result that opium trade was permitted (Macht, 1915).

Medicinal use of opium was stimulated by the famous physician Paracelsus at the end of the middle ages by the introduction of tincture of opium or laudanum. The name laudanum is probably derived from the Latin "laudandum", which means something to be praised. Several preparations of laudanum were made, all of which contained more or less opium and many other ingredients. Laudanum and other preparations of opium (e.g., extracts of opium and pilulae opii) were widely used for a number of indications. In the beginning of the 19th century, the pharmacist Sertürner isolated an important active principle of opium, the alkaloid morphine (Sertürner, 1806). Morphine was named after the Greek god of dreams, Morpheus. During the nineteenth century many other alkaloids were isolated from opium, some of them with a comparable, but weaker action than morphine and others with a different pharmacological profile. From the mid-nineteenth century on, morphine was parenterally administered as premedication for surgical procedures and for postoperative and chronic pain.

Morphine appeared to be as addictive as opium. This stimulated research to develop nonaddictive opiates, substances with the beneficial therapeutic actions of morphine but lacking its addictive potential. In 1898, heroin was introduced as the ideal nonaddictive substitute for morphine. It lasted quite a long time before it became clear that heroin has a higher addictive potential than morphine. Several claims for nonaddictive opiates followed, but to date, none of these claims have been substantiated. During the 20th century a number of drugs were synthesized with a morphine-like action, but with a structure somewhat different from that of morphine. Examples are meperidine (1939) and methadone (1946). Structure-activity studies with the morphine molecule as starting point resulted in the synthesis of nalorphine, a mixed agonist-antagonist: the drug reverses the typical actions of morphine and it precipitates the abstinence syndrome in opiate addicts, but it also has analgesic properties. Additional research led to the discovery of pure opiate antagonists such as naloxone.

B. Opioid Receptors and Endogenous Opioids

The structural similarities between all substances with an opiate-like action and the discovery of opiate agonists, mixed agonist-antagonists and antagonists, generated the concept of opiate receptors. Goldstein et al. (1971) used radiolabeled levorphanol to discover opiate-binding sites in subcellular fractions of mouse brain. When radioligands with high specific activity became available, stereospecific opiate-binding sites in the central nervous system were demonstrated (Pert and Snyder, 1973; Simon et al., 1973; Terenius, 1973). The finding of opiate-binding sites and the fact that opiate antagonists exerted some intrinsic activity in opiate naive subjects and could diminish nondrug-induced analgesia stimulated thoughts about endogenous compounds with opiate-like action (Lasagna, 1965; Jacob et al., 1974; Akil et al., 1976; Buchsbaum et al., 1977).

In this review, the term opioid will be used for all substances with an opiate-agonistic action. Endogenous and exogenous opioids can be distinguished, depending on whether the substances are normally present in the body or not. The first indication for endogenous opioids came from studies showing that brain extracts contain opioid-like activity (Terenius and Wahlström, 1974; Kosterlitz and Waterfield, 1975). Further investigations led to the isolation and characterization of the enkephalins (from the Greek "in the head"), the first discovered endogenous opioids (Hughes et al. 1975). There appeared to be two pentapeptides, Met- and Leu-enkephalin. The structure of Met-enkephalin was also present as the N-terminal part of the earlier isolated C fragment, part of the fat-mobilizing

pituitary hormone β-lipotropin (Bradbury et al., 1976). The C fragment, later termed β-endorphin (from endogenous morphine), and the enkephalins were shown to induce similar actions as morphine in a number of in vitro and in vivo test procedures. Repeated administration of β-endorphin led to tolerance to its analgesic action and to morphine-like withdrawal symptoms upon a challenge with naloxone (Van Ree et al., 1976; Wei and Loh, 1976). Furthermore, β-endorphin and the enkephalins were self-administered by laboratory animals, indicating the rewarding properties and addictive potential of these substances (Belluzzi and Stein, 1977; Van Ree et al., 1979; Goeders et al., 1984). Thus, the endogenous opioids may share all its typical opioid-like actions with morphine, both after acute and chronic administration.

After the discovery of another class of endogenous opioids, the dynorphins, (dyn. . . . from Greek dynamis = power) (Goldstein et al., 1979, 1981), it appeared that most endogenous opioids are generated by enzymatic processing from three precursor molecules, pro-opiomelanocortin (POMC),[2] proenkephalin (ProEnk), and prodynorphin (ProDyn) (Nakanishi et al., 1979; Kakidani et al., 1982; Noda et al., 1982). Each of these precursors has an unique anatomical distribution throughout the central nervous system (CNS) and in peripheral organs (Akil et al., 1984; Khachaturian et al., 1985). The anterior and neurointermediate lobes of the pituitary gland are major sites of POMC biosynthesis. In the brain, there are two distinct nuclei that contain POMC neurons: the arcuate nucleus of the hypothalamus and the nucleus tractus solitarius. Widespread projections from these neurons are present throughout the brain. From POMC the opioid β-endorphin is generated, but also α- and γ-endorphin and several nonopioid peptides, e.g., adrenocorticotropin and β- and γ-melanocyte-stimulating hormones. ProEnk-containing neurons are widely distributed throughout the brain and consist of both local circuits and long projection neurons. ProEnk is the source of Leu- and Met-enkephalin and several extended forms of these pentapeptides. ProDyn-containing cell bodies have a characteristic widespread distribution throughout the CNS. ProDyn-containing neurons have both short and long projection pathways and

can generate several opioid peptides, including α- and β-neoendorphin, dynorphin A, and dynorphin B.

Martin et al. (1976) first postulated the existence of multiple types of opioid receptors. Based on their behavioral and neurophysiological findings in the chronic spinal dog, they distinguished between the μ type (for morphine, which induces analgesia, hypothermia, and meiosis among others), the κ-type (for ketocyclazocine, which induces depression of flexor reflexes and sedation among others), and σ-type (for SKF10,047 or N-allylnormetazocine, which induces tachycardia, delirium, and increased respiration among others). Later, a fourth type of opioid receptor, named δ (for vas deferens) was identified (Lord et al., 1977). Additional research revealed that the σ-type receptor is nonopioid in nature, leaving three main type of opioid receptors, μ, δ, and κ (Mannalack et al., 1986). These receptors, belonging to the family of seven transmembrane G protein-coupled receptors, have been cloned using molecular biological techniques (Evans et al., 1992; Kieffer et al., 1992; Reisine and Bell, 1993; Uhl et al., 1994; Knapp et al., 1995). Apart from occurring as separate molecules, brain μ- and δ-opioid receptors have also been suggested to function as a μ-δ receptor complex (for review, see Rothman et al., 1993). In slices of rat neostriatum, activation of this complex, which displays an affinity profile for opioid ligands different from nonassociated μ- and δ-opioid receptors, has been shown to inhibit dopamine (DA) D1-receptor-stimulated adenylate cyclase activity (Schoffelmeer et al., 1992, 1993).

Interestingly, there seems to be some preference for the different endogenous opioid ligands for the different receptors: β-endorphin for μ, enkephalins for δ, and dynorphins for κ. Subtypes of these receptors have been proposed (μ_1, μ_2; δ_1, δ_2; κ1, κ2, κ3) (Dhawan et al., 1996) and some evidence is available for some other receptor types [e.g., the ε receptor which was labeled as β-endorphin specific (Wüster et al., 1979; Narita and Tseng, 1998)]. The International Union of Pharmacology subcommittee on opioid receptors has proposed another terminology to distinguish the opioid receptors: OP1, OP2, and OP3 for the δ, κ, and μ receptor, respectively (Dhawan et al., 1996) (Table 1). Another opioid-like receptor has been cloned, termed the ORL-1 opioid receptor (Fukuda et al., 1994; Mollereau et al., 1994; Lachowitz et al., 1995). In addition, some novel endogenous opioids have been isolated, termed orphanin FQ which seems to be an endogenous ligand for ORL-1 and endomorphin-1 and endomorphin-2 which have been pro-

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[2] Abbreviations: POMC, pro-opiomelanocortin; 5-HT, 5-hydroxytryptamine (serotonin); ICSS, intracranial electrical self-stimulation; 6-OHDA, 6-hydroxydopamine; i.c.v. intracerebroventricular; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; βE-IR, β-endorphin immunoreactivity; LAAM, l-α-acetylmethadol; LH, lateral hypothalamus; BNTX, 7-benzylidenenaltrexone; MFB, medial forebrain bundle; CCK, cholocystokinine; NAC, nucleus accumbens; CNS, central nervous system; NMDA, N-methyl-D-aspartate; CTOP, D-Phe-Cys-Tyr-D-Trp-Orn-Thr- Phe-Thr-NH₂; nor-BNI, norbinaltorphimine; DA, dopamine; ProEnk, pro-enkephalin; DAMGO, [D-Ala, N-Me-Phe[4], Gly-ol[5]]-enkephalin; PAG periaquaductal gray; DNQX, 6,7-dinitroquinoxaline-2,3-dione; ProDyn, pro-dynorphin; DPDPE, [D-Pen[2], D-Pen[5]]-enkephalin; TIQ, tetrahydroisoquinoline; VTA, ventral tegmental area; FR, fixed-ratio; HAD, high alcohol-drinking; AA, alko alcohol; DG-AVP, desglycinamide[9]-[Arg[8]]-vasopressin.

TABLE 1
Nomenclatures of opioid receptors (IUPHAR recommendations)

Preferential Endogenous Opioid Ligands	Opioid Receptors		
	IUPHAR Recommendation	Pharmacology Nomenclature	Molecular Biology Nomenclature
Enkephalins	OP1	δ	DOR
Dynorphins	OP2	κ	KOR
β-endorphin	OP3	μ	MOR

See Dhawan et al. (1996).

posed to represent a highly specific endogenous ligands for the μ receptor (Meunier et al., 1995, Reinscheid et al., 1995; Zadina et al., 1997). Since the discovery of orphanin FQ/nociceptin released the ORL-1-opioid-like receptor of its orphan status, a novel nomenclature of this receptor and its endogenous ligand has been proposed. By analogy to the known opioid receptors (μ, δ, and κ) the new name for ORL-1 would be o (omicron), after its endogenous ligand (orphanin). Metonymorphin, xenorphin, or endomicron were proposed as possible new names for orphanin FQ/nociceptin (Henderson and McKnight, 1997). It should, however, be noted that, if orphanin FQ/nociceptin were given a new name, then the possible new name for ORL-1 would change as well. We suggest the use of the combination xenorphin/ξ receptor and consequently XOR and OP4 for the molecular biology and International Union of Pharmacology recommendation nomenclature, respectively (Table 1).

C. Addiction

Opioids are drugs used for pain relief, against dysentery, and for a number of other therapeutic indications. During repeated treatment, tolerance to certain effects of opioids develops, e.g., to their analgesic action, which could result in discontinuation of the treatment, either or not after an increase of the daily dose. Another phenomenon occurring upon repeated treatment is the induction of physical dependence, characterized by withdrawal symptoms after discontinuation of drug treatment. Pathognostic for withdrawal symptoms is that they are suppressed by administration of the drug. Thus, the presence or the expectation of withdrawal symptoms could be an important incentive for restart or continuation of drug use. Although this does not seem to be a major problem in clinical practice, withdrawal symptoms have dominated postulates about the underlying mechanisms of addictive behavior for a long time.

It was generally believed that addicts will initiate their drug-taking habit because of the inherent euphoric action of opioids and will continue their habit to prevent the occurrence of withdrawal symptoms. Therefore, most addiction research was directed at the underlying mechanisms of physical dependence and related withdrawal symptoms. In this framework, drug-taking behavior has been conceptualized in the context of drive reduction (Hull, 1943). There emerged, however, some problems with this concept. The relapse rate in opioid addiction is high, also when the withdrawal symptoms have already disappeared for a long time. Moreover, physical dependence also develops in patients treated with opioids, for example, pain relief, but the percentage of these patients that initiates addictive behavior is quite low. Furthermore, physical dependence hardly develops with some other drugs with high-addictive potential such as cocaine. These observations stimulated research to delineate other factors that could explain the development and maintenance of opioid addiction and

drug addiction in general. Among these are the reinforcing properties of drugs, drug-induced craving, and the concept of psychic dependence. During the last decades, several consensus meetings have been organized to provide workable terminology and concepts. However, in the literature of today, the terms addiction, dependence, and drug abuse are still used interchangeably.

Drug abuse may refer to "the use, usually by self-administration, of any drug in a manner that deviates from the approved medical or social patterns within a given culture" (Jaffe, 1990). Drug dependence may be a syndrome manifested by a behavioral pattern in which the use of a given psychoactive drug or class of drugs is given much higher priority than other behaviors that once had higher value. In its extreme form drug dependence is associated with the need for continued drug exposure (compulsive drug use), and it exhibits the characteristic of a chronic relapsing disorder (Edwards et al., 1981). Addiction can be regarded as a severe degree of drug dependence that is an extreme on the continuum of involvement with drug use (Jaffe, 1990). The system of diagnosis for mental disorders published in DSM-IV by the American Psychiatric Association (1994) uses the term substance dependence instead of addiction for the overall behavioral syndrome. Substance dependence is defined as "a cluster of symptoms indicating that the individual continuing use of the substance despite significant substance-related problems". Withdrawal symptoms and tolerance can be present but are not a conditio sine qua non for the diagnosis substance dependence. Substance abuse, a less severe diagnosis, involves a pattern of adverse consequences from repeated use that does not meet criteria for substance dependence (O'Brien, 1996).

The need for continued drug use in drug dependence and addiction is basically of a psychic nature. Psychic dependence has been defined by "a condition in which a drug produces a feeling of satisfaction and a psychic drive that requires periodic or continuous administration of the drug to produce pleasure or to avoid discomforts" (Eddy et al., 1965). Besides development of psychic dependence, physical dependence ["an adaptive state that manifests itself by intense physical disturbances when the administration of the drug is suspended" (Eddy et al., 1965)] can contribute to compulsive drug use but it is not necessary for continued use. Although the nature of psychic and physical dependence is different, both are considered a priori to result from adaptive changes of neural systems in the brain in response to repeated drug use and/or exposure.

With regard to use of drugs, there exists a continuum from no drug use via controlled use to an actual dependence on the drug. The transition from controlled use to dependence may be referred to as initiation of drug dependence. It has been suggested that initially the use of a particular drug is related to its ability to produce effects of well being and euphoria. Environmental vari-

ables and/or individual characteristics contribute to whether or not an individual becomes dependent on the drug. At this point a basic emotional feature may have been altered by repeated drug use, which in turn is responsible for the need to experience the effect of the drug again and again. This need is basically of a psychic nature, but it can contain physical elements such as physical dependence. Once a person has become dependent on a drug, discontinuation of drug use is difficult. Even after a prolonged period of abstinence, addicts can relapse into their former habit of drug dependence. A factor that may be important for relapse is craving, a (intense) desire to re-experience the effects of the drug (Rankin et al., 1979; Markou et al., 1993). Drug craving can be conceptualized as the incentive motivation to self-administer a previously consumed drug. This craving may be present during continuous use of the drug and long after abstinence, and may develop on basis of incentive sensitization mechanisms in which associative learning plays a role (Bolles, 1975; Stewart et al., 1984; Robinson and Berridge, 1993). Besides craving, other factors may contribute to relapse, which is the major target for treatment programs of drug addiction.

II. Reinforcement and Motivation

Alterations in the organism's environment trigger sensory mechanisms and thus generate information that is conveyed to the CNS. This information and other inputs into the brain are integrated at several levels and can activate or inhibit the brain output systems, including motor systems, thus eliciting behavioral changes. The purpose of these behavioral changes is the adaptation of an organism to changes in environmental conditions, with the ultimate result that survival of the organism or its species is ensured. The extreme of an environmental continuum is that the organism approaches a desirable (pleasant) and avoids a noxious (aversive) environment.

The setpoint of behavioral reactions is determined by genetic factors but its value is being modulated continuously by new experiences and, as a consequence, by acquired behavioral patterns. Behavioral reactions can be acquired through the association of stimuli that are originally neutral to innate reactions. The processes involved are types of associative learning. Forms of nonassociative learning include habituation and sensitization. During habituation, the reflex reaction elicited by a nonnoxious stimulus decreases when the stimulus is presented repeatedly. Sensitization involves an increased reflex reaction to a wide range of stimuli given shortly after the presentation of an intense or noxious stimulus. Through nonassociative learning the organism learns about the properties of one particular stimulus.

Two major classes of associative learning are distinguished: classical and instrumental conditioning. During classical conditioning, a concept which was introduced by Pavlov (1927), the organism learns about the relationship between one stimulus in its environment and another stimulus (the unconditioned and the "neutral" conditioned stimulus). The unconditioned stimulus activates an established reflex and thus elicits an unconditioned reaction (e.g., the presence of food in the mouth results in salivation). Before conditioning the conditioned stimulus does not elicit the unconditioned reaction. After association of the conditioned stimulus and the unconditioned stimulus, the conditioned stimulus evokes a conditioned reaction that resembles the unconditioned one (e.g., when a sound is presented repeatedly, either immediately before or while food is in the mouth, salivation will ultimately follow after the presentation of the sound). Classical conditioning allows the organism to predict the coherence between events in its environment. The conditioned stimulus has become an anticipating signal for the occurrence of the unconditioned stimulus. The conditioned response can prepare the organism to deal with the result of the unconditioned stimulus more efficiently.

Instrumental conditioning, introduced by Thorndike (1913), refers to the process of learning about the relationship between a stimulus and the behavior of the organism. When a certain behavioral act is followed by a favorable change in its environment, the organism tends to repeat this behavior (law of effect). This change in environment can be the occurrence of a pleasant stimulus or the removal of an aversion or noxious stimulus. In instrumental conditioning, in contrast to classical conditioning, the (behavioral) response changes the probability that the unconditioned stimulus will appear, allowing the organism to have more or less control over its environment. Four types of instrumental conditioning can be distinguished: positive reinforcement (presentation of a pleasant stimulus), punishment (presentation of an aversive stimulus), negative punishment (removal of a pleasant stimulus), and negative reinforcement (removal of an aversive stimulus). The frequency of behavioral responses usually increases when positive or negative reinforcement is operative and decreases in the case of punishment, including negative punishment.

Many studies on positive reinforcement in experimental animals use lever manipulation as the behavioral response, and the conditioning in such experiments is also termed operant conditioning. This type of conditioning is often investigated in the so-called "Skinner box" (Skinner, 1938). A typical experiment involves placement of a hungry animal in a box in which a horizontal lever protrudes from a wall. Pressing the lever is followed by presentation of food. The animal learns that this behavioral act is reinforced by food. Thus, when the animal is hungry and is placed in the same box it is likely to press the lever to obtain food. The behavioral act in operant conditioning is termed "operant", and the pleasant stimulus that tends to increase the frequency of the operant is called "positive reinforcer".

Operant conditioning has had a major influence on addiction research and contributed to the concepts in this field. Using the *drug self-administration* paradigm, it was shown that most if not all abused drugs could serve as positive reinforcer. Another reinforcement-related property of drugs of abuse is the ability to potentiate the effectiveness of other rewards. The effects of drugs of abuse on the reinforcing effects of *intracranial electrical self-stimulation* (ICSS) offers a useful model to quantify such property. Besides positive reinforcing effects drugs of abuse have other motivational properties and even may induce a central motivational state. In addition, drugs of abuse are able to confer their positive motivational properties to environmental cues through classical conditioning processes, which in turn, by facilitating successful contact with the drug stimulus, could contribute to drug addiction. The self-administration procedure allows to study certain drug-induced motivational processes, such as craving, using specific methodology like progressive ratio, choice, extinction, conditioned reinforcement, and second-order schedule procedures (Markou et al., 1993). Animal models in which the motivational properties of drugs of abuse can be quantified and in which the drug is investigated, but not self-administered, are, for example, the *conditioned place preference* and the second-order schedule paradigm. In addition, other properties of the drug such as the discriminative stimulus properties may contribute to the drug use habit. The *italicized* animal models of drug dependence will be discussed in more detail.

In literature, the concepts of reward and of (positive) reinforcement are often used in describing effects of drugs of abuse. These terms carry different meanings, however, in the sense that reward implies a positive subjective effect of a stimulus, whereas positive reinforcement is strictly a measure of the beneficial effect of a stimulus on acquisition or frequency of a required behavioral response. Thus, whereas reinforcement can be assessed experimentally, reward is a matter of interpreting experimental findings. In translation to drugs of abuse, reward implies the positive subjective effect of the drug and positive reinforcement the facilitating effects of a drug on the learning of a required behavioral response.

A. Self-Administration

Drug self-administration is the most widely used model for the experimental analysis of drug addiction and is based on the concepts of operant conditioning. The administration of a drug of abuse is made contingent upon a behavioral response of the animal. This response may consist of alleyway running, arm choice in Y-maze and drinking of flavored solutions, yet most studies use lever-pressing as the behavioral act. An increase in the frequency of the response provides evidence that the drug is self-administered, and thus serves as a positive reinforcer.

In 1940, Spragg (1940) first suggested that drugs could function as positive reinforcers. His suggestion was based on experiments with chimpanzees, which were made physically dependent on morphine by daily treatment with morphine for several months. Then the animals could learn to select one of two boxes concealing a syringe filled with a morphine solution, which would subsequently be administered to the animal by the experimenter. The monkeys opened the box containing the morphine syringe more often than the other box that contained food.

Self-injection by animals was first reported by Headlee et al. (1955), who demonstrated that morphine was injected i.p. by physically dependent rats. In the early 1960s, several investigators developed techniques for i.v. self-administration in rats and monkeys (Weeks, 1962; Thompson and Schuster, 1964). Typically, an animal is surgically prepared with a chronic, indwelling i.v. catheter, which is guided s.c. to the arm, back, or head. Depending on whether primates or rodents are tested, restrainment in the test cages is used. Whereas monkeys are usually restrained by a primate chair or harness and arm arrangement, rats are allowed to move about freely in the test cage. The i.v. catheter is connected with an automatic infusion pump. Intravenous drug injections are made contingent upon a certain behavioral response under specified schedules of reinforcement.

Initial research with the i.v. self-administration method demonstrated that both opioid-dependent and opioid-naive animals would press a lever to receive injections with morphine (Weeks, 1962; Thompson and Schuster, 1964; Deneau et al., 1969). It became clear that besides morphine a wide variety of psychoactive drugs from different pharmacological classes could serve as positive reinforcers in animals. These drugs include psychomotor stimulants, such as amphetamine and cocaine (Pickens and Harris, 1968; Pickens and Thompson, 1968; Van Ree et al., 1978), dissociative anesthetics, such as barbiturates and benzodiazepines (Davis et al., 1968; Pilotto et al., 1984), ethanol (Smith and Davis, 1974), Δ^9-tetrahydrocannabinol and the cannabinoid receptor agonist WIN 55,212 (Van Ree et al., 1978; Takahashi and Singer, 1979; Martellotta et al., 1998), phencyclidine (Balster and Woolverton, 1980), and nicotine (Lang et al., 1977; Goldberg and Spealman, 1982). In general, drugs that are self-administered by animals are abused to some extent by humans although there are exceptions. For example, rats will readily self-administer apomorphine (Baxter et al., 1974; Colpaert et al., 1976), whereas humans will not become dependent on this drug because of its nausea-promoting effects. Conversely, drugs that fail to initiate or maintain self-administration behavior in animals have no or little abuse potential in humans. It should, however, be noted that not all drugs are equally powerful as positive reinforcers in animals. For instance, nicotine is self-administered under a narrower unit dose range than opioids and cocaine. Nonetheless, the drug

self-administration model can serve as a useful model for the prediction of the abuse potential of drugs in humans (Thompson and Young, 1978; Van Ree et al., 1978; Van Ree, 1979; Collins et al., 1984).

Intravenous self-administration in rats and monkeys is the most frequently used to assess the reinforcing effects of drugs. However, other models using other species (e.g., dogs, cats, mice, or pigeons) or other routes of administration (e.g., intragastric, oral, inhalation, i.c.v., or intracerebral) have been developed (e.g., Smith et al., 1976; Jones and Prada, 1977; Carroll and Meisch, 1978; Van Ree and Niesink, 1978; Van Ree et al., 1979; Kilbey and Ellinwood, 1980; Van Ree and De Wied, 1980; Bozarth and Wise, 1981b; Criswell, 1982; France et al., 1991; Mattox and Carroll, 1996).

Although the positive reinforcing effects of a drug are the most important stimuli in self-administration behavior, other factors may contribute significantly to operant behavior and thus self-administration behavior. These factors include, among others, conditioned or secondary reinforcement and negative reinforcement. Distinctive, neutral environmental stimuli that are repeatedly associated with the primary reinforcing effects of a drug, can acquire (secondary) reinforcing properties through classical conditioning (Davis and Smith, 1976; Beninger, 1983; Stewart et al., 1984). These stimuli are then called conditioned or secondary reinforcers. Although the primary reinforcing effects of the drug mainly determine the initiation of self-administration behavior, the conditioned or secondary reinforcers maintain this behavior over time, even in the absence of the primary reinforcer. For example, a red light switched on when a monkey presses a lever to obtain a morphine injection subsequently supports lever-pressing when morphine is temporarily not available (Schuster and Woods, 1968). The effects of conditioned reinforcers diminish over time when the drug injection is no longer available. In animals made physically dependent on drugs, an additional factor influencing self-administration behavior is exerted by negative reinforcement, i.e., the animals will continue to self-administer a drug to alleviate or overcome the presumably aversive (negative) state of withdrawal (Solomon, 1980; Koob et al., 1989a).

B. Intracranial Electrical Self-Stimulation

Intracranial electrical self-stimulation (ICSS) is widely used to explore the involvement of particular brain circuits in reward. Typically, when an animal is equipped with an electrode placed in a "positive" brain area and given the opportunity to perform a behavioral response, e.g., pressing a lever, that is followed by a short-pulse train of electrical current via the electrode, the animal will initiate and maintain responding. Thus, the stimulation serves as an operant reinforcer (Skinner, 1938). The phenomenon of ICSS has been described initially by Olds and Milner (1954), who observed this behavioral pattern in rats equipped with electrodes in the septal area of the brain. ICSS was suggested to be

linked to brain circuits implicated in natural incentives such as food and sexual contact (Olds and Milner, 1954; Trowill et al., 1969; Mogenson and Wu, 1982). However, it appeared that a variety of brain structures, related and not related to natural incentives, could support ICSS (Olds et al., 1971; Wise, 1996). Although ICSS resembles other types of reward, it has some unique properties. In most stimulated sites, the rewards are strong and immediately present during stimulation and it lasts not much longer than the stimulus itself. The brain structures in which ICSS can be elicited have been designated as reward or pleasure centers. Whether these various brain structures belong to a single system or to multiple reward circuits operating in parallel is still a matter of debate.

In general, drugs of abuse facilitate ICSS in that the frequency current-response function is shifted leftward in a parallel manner and/or the threshold for eliciting ICSS is decreased. Such findings have been documented for morphine and heroin (Esposito and Kornetsky, 1977; Van Wolfswinkel and Van Ree, 1985b; Hubner and Kornetsky, 1992; Bauco et al., 1993), amphetamines (Gallistel and Karras, 1984; Schaefer and Michael, 1988b), cocaine (Bain and Kornetsky, 1987; Frank et al., 1988; Van Wolfswinkel et al., 1988; Bauco and Wise, 1997), nicotine (Huston-Lyons et al., 1992; Bauco and Wise, 1994; Ivanova and Greenshaw, 1997; Wise et al., 1998), phencyclidine (Kornetsky and Esposito, 1979; Carlezon and Wise, 1993b), and Δ^9-tetrahydrocannabinol (Gardner et al., 1988, 1989; Lepore et al., 1996). With respect to ethanol, the data so far are not fully consistent (De Witte and Bada, 1983; Schaefer and Michael, 1987; Bain and Kornetsky, 1989, Moolten and Kornetsky, 1990; Lewis and June, 1994). It seems that facilitation of ICSS is an effect that drugs of abuse have in common, despite the differential pharmacological characteristics of these drugs. Thus, facilitation of ICSS may be relevant for the dependence-creating properties of drugs and worthwhile to analyze in detail to understand the basic mechanisms of drug dependence.

Concerning the neurobiology of ICSS, catecholamines and especially DA have been implicated as important neurotransmitters in the reward circuit (Crow, 1972; German and Bowden, 1974; Wise, 1978). Evidence that DA is involved in ICSS stems from anatomical studies (Corbett and Wise, 1980), lesion experiments (Fibiger et al., 1987), pharmacological manipulations (Zarevics and Setler, 1979; Wise and Rompré, 1989), and neurochemical studies (Nakahara et al., 1992; Fiorino et al., 1993; Di Chiara, 1995). It has been suggested that in particular the mesocorticolimbic DA system is important for ICSS.

C. Conditioned Place Preference

Affective (rewarding or punishing) stimuli can evoke approach or avoidance behavior, respectively (Schneirla, 1959). When these stimuli are paired with a neutral

environment, these neutral environmental stimuli can gain the capacity of evoking similar approach or avoidance behavior as the affective stimulus (Pavlov, 1927). Affective effects of drugs can thus be assessed by giving the animal the possibility to express attraction or aversion to environments paired with effects of drugs. This principle is the basis of the place-conditioning method. In place-conditioning, individuals are exposed to distinctive neutral environmental cues as conditioning stimulus, after being treated with a drug, the effects of which will then act as an unconditioned stimulus (Hoffman, 1989; Schechter and Calcagnetti, 1993; Bardo et al., 1995). A test apparatus, consisting of (at least) two compartments with distinct visual, olfactory, or tactile cues is used, so that an animal will be able to distinguish between these compartments. In alternating conditioning sessions, the animal is confined to one compartment after being injected with a drug. In a subsequent session, the animal is injected with placebo and placed in the other compartment. This procedure is repeated several times [although significant place-conditioning can be achieved with a single conditioning session (Mucha et al., 1982; Bardo and Neisewander, 1986)] so that the animal learns to associate the cues of one distinct compartment of the test apparatus with the effects of the test drug. On a day after these conditioning sessions, the animal is placed in the test apparatus, without any confinements. The animal will have the opportunity to move freely around the different compartments, and the relative amount of time spent in these compartments is measured. When the animal spends significantly more time in the drug-paired part of the apparatus, it is said to display conditioned place preference. Likewise, a smaller amount of time spent in the drug-paired environment reflects conditioned place aversion.

With respect to conditioned place preference, there are some experimental variables that need to be taken account of. First, the structure of the place-conditioning apparatus may be such that an animal has an initial preference for one or the other compartment. If, for example, an apparatus consisting of a black and a white compartment is used, rats usually have a natural preference for the black (i.e., darker) side of the apparatus. Such preference may be revealed by subjecting the animals to a pretest before conditioning commences. In this case, termed a biased design, the conditioning drug of which a preference is expected is mostly paired with the least preferred compartment of the apparatus. Place-conditioning is then expressed as the amount of time spent in the drug-paired compartment of the test apparatus minus the amount of time spent in that environment during the pretest. A criticism on the biased design is that approach behavior might not be due to positive motivational but to anxiolytic properties of the drug, decreasing the animals' anxiety in a nonpreferred environment. However, the finding that place preference even in an biased design is consistently found with psy-

chostimulant drugs such as amphetamine and cocaine, which do have anxiogenic properties, is hard to reconcile with such reasoning. An alternative experimental design is to pair the conditioning drug with one side of the apparatus in half of the animals and with the other side in the other half of the animals (counterbalanced design). The most elegant approach is to manipulate the different environments in such a way using, for example, different odors that animals no longer prefer one side of the apparatus over the other (unbiased design), and to subsequently condition the animals in a counterbalanced fashion. A second factor is that the effects of a conditioning drug might interfere with exploration of the drug-paired environment. Since environmental novelty can elicit both approach and avoidance behavior, this might influence the expression of conditioned place preference or aversion. To circumvent this, a place-conditioning apparatus consisting of three compartments can be used. Two parts of this apparatus will then be paired with placebo or drug, respectively, whereas the third compartment is completely novel to the animal on the test day. The presence of a novel compartment might then obviate for any influences of exploratory behavior on preference for the placebo- or drug-paired environment, supposedly overruling the relative novelty of one of the two conditioning compartments. Environmental novelty has been shown to elicit conditioned place preference (Bardo et al., 1989) and the capacity of novelty to induce place preference has also been compared with drug-induced place preference. It was shown that rats consistently preferred environments paired with morphine, amphetamine, or apomorphine over novel environments, which were in turn preferred over familiar, saline-paired environments (Parker, 1992).

Place-conditioning studies have been performed with a wide variety of psychoactive drugs as well as with nonpharmacological stimuli. For example, conditioned place preference has consistently been observed using opioids such as morphine, fentanyl, heroin, and β-endorphin, psychostimulants, e.g., amphetamine, methylphenidate, cocaine, 3,4-methylenedioxymethamphetamine ("ecstasy"), and nicotine, as well as with benzodiazepines such as diazepam. In addition, nonpharmacological cues such as social and sexual interaction, environmental novelty, and sucrose drinking elicit conditioned place preference. Place aversion has been reported for opioid antagonists such as naloxone, for lithium chloride, and for aggressive attacks, ionizing radiation, and footshock. Mixed results have been reported for apomorphine, caffeine, ethanol, and phencyclidine (for reviews, see Hoffman, 1989; Schechter and Calcagnetti, 1993).

The place-conditioning paradigm has some interesting properties in comparison to other models generally used in addiction research. First, next to positive motivational, also aversive properties of drugs can be assessed. This is also possible with the self-administration method. In that case, the number of self-injections with

the drug with aversive effects will be lower than the number of placebo self-injections. To observe these aversive effects, however, relatively high levels of responding for placebo will be required, whereas in the place-conditioning method there is no such restriction. Second, the place-conditioning paradigm is not an operant task, but rather a classical (Pavlovian) conditioning paradigm. During conditioning, the drug will be delivered, irrespective of the behavior of the animal. What is learned is therefore not response conditioning but stimulus conditioning. However, what is measured during testing is not merely the result of classical conditioning because the approach behavior that is measured is not necessarily part of the primary (unconditioned) response of the animal to the drug. Third, the behavior of the animal is measured in the drug-free state. Any drug effects that might interfere with behavioral performance during testing is avoided. However, testing animals in a drug-free state is also a disadvantage. Since conditioning and testing are conducted in two different interoceptive states, state-dependent learning might occur, causing a risk of false negatives. Finally, since significant place-conditioning can be obtained with a small number of conditioning trials, the duration of the experiments is relatively short.

The most serious disadvantage of the place-conditioning technique is that the interpretation of data is difficult. As most if not all substances that are self-administered by humans and laboratory animals also have the property to induce conditioned place preference, it is suggested that their positive affective properties play a significant role in the development of place preference. It is, however, hard to interpret what the animal is exactly expressing with its approach or avoidance behavior. The most likely explanation is that conditioned place preference reflects the desire to experience the effects of the drug. However, since in most cases only time spent in a certain compartment is scored, such a conclusion cannot definitely be drawn.

III. Self-Administration

A. Intravenous Opioid Self-Administration

The first studies on i.v. opioid self-administration were performed in the 1960s. Different groups demonstrated that rhesus monkeys and rats would learn to press a lever to receive i.v. infusions with morphine (Weeks, 1962; Thompson and Schuster, 1964; Deneau et al., 1969). These experiments showed that morphine served as a positive reinforcer of self-administration behavior in animals made physically dependent on opioids as well as in animals which were naive to the drug (nondependent). These initial experiments have been replicated and extended by many laboratories over the last decades. Reviewing the studies evaluating the reinforcing properties of opioids in the self-administration paradigm revealed several procedures that could be classified under different headings. In the present overview,

we divide them into the "acute" method and the "substitution" method.

In the first method, the acute method, the animal is allowed access to the test drug without previous experience with this drug or any standard drug. Different procedures can be applied. For example, the animal is given initial access to vehicle (usually saline) for a few days to obtain control rates of responding before being offered the test drug. Alternatively, the animal is initially trained to lever-press for a nondrug reinforcer (usually food pellets) on a continuous reinforcement schedule to familiarize the animal with lever-press responding. In a third procedure an animal without any previous experience with the behavioral requirements for the delivery of the drug is offered access to the test drug. During the period of actual access each lever-press results in an infusion. The acute method is useful in assessing whether an animal will initiate self-administration of the test compound, whether responding for the compound will change over time, and to assess dose-response curves of the test compound.

In the substitution method, drug self-administration is first established with a standard compound known to be reinforcing. In short, during daily experimental sessions, animals are trained to respond for an i.v. delivery of a standard compound. This compound is referred to as baseline drug and is known to produce reliable self-administration rates over sessions. In substitution studies evaluating the reinforcing properties of opioids, codeine, a pure opioid agonist, is mostly used as baseline drug, although some studies use cocaine as such. After responding becomes stable, a dose of a test compound or vehicle (usually saline) is substituted for the baseline drug for one or several sessions. If saline is substituted, responding tends to decline to relatively low rates (negative control). On the other hand, when a test compound is substituted, the compound may maintain responding at some level above that of saline. If this occurs, the drug is classified as a positive reinforcer. Using this method dose-response curves of test drugs can be generated and relative reinforcement potencies of several drugs can be determined.

The results of the opioid self-administration studies with these methods have been reviewed (e.g., Johanson and Balster, 1978; Griffiths and Balster, 1979; Woolverton and Schuster, 1983; Collins et al., 1984; Young et al., 1984; Balster and Lukas, 1985; Vaupel et al., 1986; Woods and Winger, 1987). In the next paragraphs, we summarize the early findings and refer to previous reviews for more detailed discussion.

Johanson and Balster (1978) summarized data generated using the substitution method in monkeys to assess the reinforcing properties of several opioid drugs. They reported that, in general, all tested pure opioid agonists are readily self-administered under a variety of experimental protocols. These agonists include the opioid agonists l-α-acetylmethadol (LAAM), alfentanil, codeine, dihydroetorphine, etonitazine, etorphine, fentanyl, heroin,

hydromorphone, levorphanol, methadone, meperidine, morphine, and propoxyphene (Ternes et al., 1985; Bertalmio and Woods, 1989; Beardsley and Harris, 1997). An exception was the opioid agonist tilidine, which acted as a positive reinforcer in one laboratory but not in another laboratory. The mixed opioid agonist-antagonists buprenorphine, butorphanol, α-etazocine, nalbuphine, pentazocine, and propiram tested in different laboratories also served as positive reinforcers in the substitution procedure. In contrast, drugs like cyclazocine, ketocyclazocine, levallorphan, nalorphine, naloxone, and naltrexone were not self-administered by monkeys (Slifer and Balster, 1983). Self-administration of opioids appeared to be stereoselective in the sense that the d-isomer dextrorphan was not self-administered, whereas the l-isomer levorphanol was (Winter, 1975). In addition i.v. self-injections have been observed with the enkephalin analog FK-33-824 in monkeys physically dependent on morphine (Mello and Mendelson, 1978).

Comparing the positive reinforcing properties of opioids with their discriminative and antagonistic effects (reversal of behavioral effects of opioid agonists and direct rate-decreasing action), a distinction can be made in three groups, i.e., opioids with morphine-like properties (μ-type opioid), opioids represented by ethylketazocine (κ-type opioid), and opioid antagonists (Woods et al., 1982; Woolverton and Schuster, 1983; Young et al., 1984; Woods and Winger, 1987). In general, preferential μ-type opioid agonists (such as alfentanil, codeine, etorphine, fentanyl, heroin, levorphanol, meperidine, methadone, and morphine) and the mixed μ-type opioid agonist-antagonists (such as buprenorphine, butorphanol, nalbuphine, pentazocine, profadol, and propiram) that exert morphine-like effects in other systems readily maintain i.v. self-administration in rhesus monkeys. In contrast, the ethylketazocine-like opioid agonists, such as bremazocine, ethylketazocine, ketacyclazocine, ketazocine, and other benzomorphan ligands, in general do not maintain self-administration behavior. Also, the mixed opioid agonist-antagonists, like cyclazocine, nalorphine, and oxilorphan, which share agonistic actions primarily with the ethylketazocine-like opioid agonists, are not self-administered by monkeys. In fact, they act as negative reinforcers in the self-administration procedure. The third group, the opioid antagonists such as naloxone and naltrexone, fails to maintain responding and in higher doses serve as negative reinforcers.

Griffiths and Balster (1979) investigated whether the self-administration paradigm could be useful as a tool in the assessment of the subjective effects of opioids in humans. For that the results of drug self-administration of the above-mentioned opioid drugs by monkeys using the substitution procedure were compared with clinical evaluations of morphine-like signs, symptoms, and subjective effects of a single dose of these opioid drugs in humans (Jasinski, 1977). Of the 33 drugs examined, 4 drugs did not produce similar results in humans and monkeys. Of these four drugs, three (i.e., dextromethorphan, butorphanol, and nalbuphine) were self-administered by monkeys but induced no or equivocal morphine-like effects in humans. One drug, tilidine, produced clear morphine-like subjective effects in humans but did not readily maintain self-administration in monkeys. The opioid antagonists were not self-administered by monkeys nor produced morphine-like effects in humans. The concordance between the human and animal results in this study validates the use of the self-administration paradigm to subjective effects of opioids in humans.

Although the monkey has been the preferred species for testing the abuse potential of new drugs, the increasing costs of this experimental animal led Collins et al. (1984) to develop a rapid screening test for the reinforcing actions of, among others, several opioid drugs in a less expensive animal, the rat. Using the acute self-administration method with drug-naive rats, they showed that the self-administration results with opioid drugs in rats paralleled those obtained with monkeys. Moreover, using drug-naive animals, these results demonstrated that opioid drugs, besides maintaining self-administration behavior, also readily initiate self-administration behavior. In rats, self-administration has been shown for μ-type opioid agonists 6-acetylmorphine, codeine, dihydroetorphine, dihydromorphine, etonitazene, fentanyl, heroin, meperidine, methadone, morphine, and propoxyphene; the mixed μ-type opioid agonist-antagonists butorphanol, nalbuphine, nalorphine, and pentazocine; and the κ-type opioids ethylketocyclazocine and ketocyclazocine (e.g., Weeks and Collins, 1964, 1979; Collins and Weeks, 1965; Smith et al., 1976; Van Ree et al., 1978; Collins et al., 1984; Young and Khazan, 1984; Dai et al., 1989; Martin et al., 1997). Furthermore, [D-Ala^2]-Met-enkephalin, dynorphin-(1–13), and [D-Ala^2]-dynorphin-(1–11) were i.v. self-administred in rats physically dependent on morphine and pretrained to self-inject morphine (Tortella and Moreton, 1980; Khazan et al., 1983). The μ-type antagonists cyclazocine and naloxone were not self-administered (Collins et al., 1984).

In more recent studies another method, the reinstatement model, has been used to assess the effects of opioids on opioid-seeking behavior. Typically, animals are trained to i.v. self-administer opioids. After reliable self-administration, extinction sessions are given during which saline is substituted for the opioid. After termination of responding under extinction conditions, a priming injection with a test drug is given and lever-pressing is assessed. Stewart and coworkers (De Wit and Stewart, 1983; Stewart, 1983) found that priming injections of 50 to 200 μg/kg heroin effectively reinstated heroin-seeking behavior in rats. Priming infusion of pharmacologically related drugs also reinstated responding on the lever associated with heroin infusions. Under these conditions, injections with nalorphine (10 mg/kg) however did not reinstate lever-press behavior

and naltrexone (2 mg/kg) suppressed responding below the levels seen after saline injections (Stewart and Wise, 1992). Using this reinstatement procedure, the same research group replicated their findings, in that reexposure to heroin after abstinence reinstated heroin-seeking behavior, whereas an injection of naloxone did not (Shaham and Stewart, 1996; Shaham et al., 1996, 1997). Moreover, they found that brief exposure to footshock stress or corticotropin-releasing hormone reinstated heroin-seeking behavior, thereby mimicking the effect of a noncontingent priming infusion of heroin, although differences may be present with regard to the neurobiology of the various reinstatement stimuli (Shaham and Stewart, 1994, 1995; Shaham et al., 1996, 1997). By contrast, the aversive state of opioid withdrawal, induced by an injection with naltrexone, did not reinstate drug-seeking behavior. Other abused drugs like amphetamine and cocaine are also capable to reinstate drug-seeking behavior in animals, previously trained to self-administer heroin (De Wit and Stewart, 1983; De Vries et al., 1998). It has been argued that the reinstatement model is relevant for assessing opioid-induced relapse.

In general, it seems that both the pure μ-opioid agonists (such as morphine, methadone, codeine, and heroin) and the mixed μ-opioid agonist-antagonists (such as butorphanol, nalbuphine, and buprenorphine) serve as positive reinforcers in the different i.v. self-administration paradigms in monkeys and rats. On the other hand, κ-opioid agonists (such as ethylketazocine, ketazocine, and benzomorphan ligands) and opioid antagonists (such as levallorphan, naloxone, and naltrexone) do not maintain self-administration behavior or even maintain responses that postpone or terminate their injection (negative reinforcers). In the rat, however, self-administration of (ethyl)ketazocine and nalorphine has been reported.

B. Variables Interfering with Opioid Self-Administration

Drug-taking behavior in general, and opioid self-administration in particular, is controlled by a number of variables. The most commonly discussed variables concern those that can readily be manipulated, e.g., the dose of the drug administered, the route of administration, the schedules of reinforcement, and the presence or absence of physical dependence, tolerance, and sensitization. In addition, a number of predisposing variables (e.g., preexposure to opioids during gestation, environmental factors, and genetic factors) can affect drug-taking behavior. The contribution of these factors will be discussed briefly. The discussion will focus on studies with rhesus monkeys and rats since the reinforcing properties of opioids have been studied most extensively in these species.

1. Dose of the Drug. The dose of the drug per injection ("unit dose") is an important and critical factor in drug-taking behavior. A linear function between the log dose

of drug delivered per injection and the amount of drug taken (Fig. 1) has been shown to exist for various opioids in different species of animals (Weeks and Collins, 1964, 1979; Smith et al., 1976; Harrigan and Downs, 1978a; Van Ree et al., 1978; Dai et al., 1989). Moreover, studying heroin self-administration, it was demonstrated that the linear relationship between the log unit dose and drug intake is present during initial exposure to heroin and in animals physically dependent on heroin (Van Ree et al., 1978; Dai et al., 1989).

An intermediate dose range is optimal for maintaining self-administration of morphine, whereas lower and higher doses do not favor it. Data from a wide range of unit doses for drug-naive rats taking i.v. morphine on a continuous schedule of reinforcement have been reported (Smith et al., 1976; Weeks and Collins, 1979). On the fifth or sixth day of self-administration, a medium dose of around 30 μg/kg morphine per infusion maintained a maximum number of i.v. deliveries. When lower doses of morphine were tested, a progressive decrease in the rate of self-administration was found, probably due
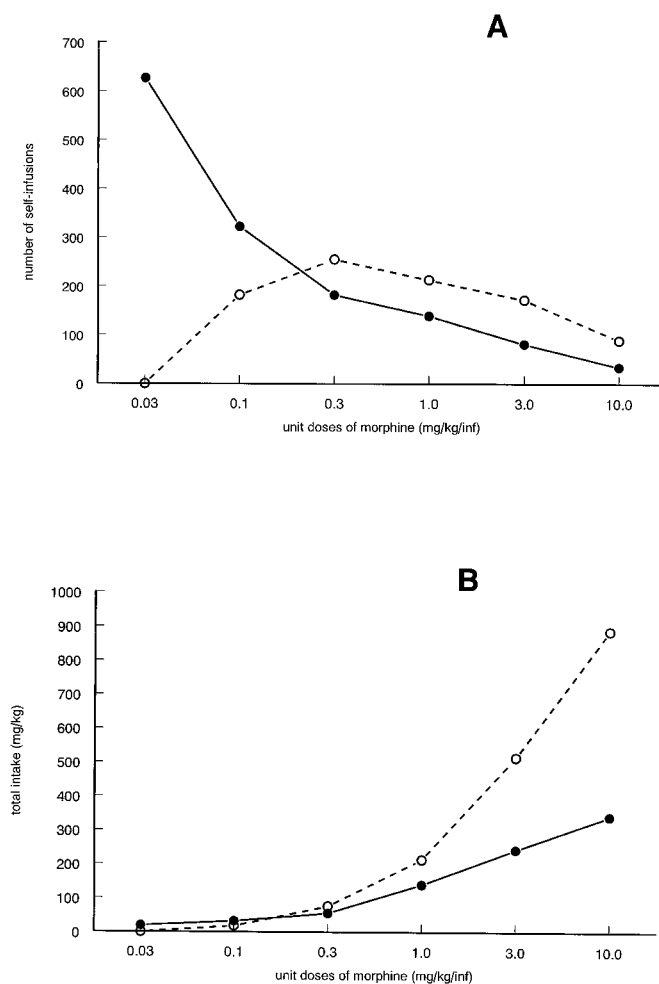

FIG. 1. Self-administration of morphine sulfate in rats. Presented are the mean number of self-infusions (A) and the mean amount of drug intake (B) by either the i.v. (●) or the intragastric route (○) versus the unit dose of morphine sulfate per infusion. Data from Smith et al. (1976).

to a decrease in reinforcing efficacy of the drug. Similarly, with higher doses of morphine [100–10,000 μg/kg/ infusion (inf)] a decrease in rate of responding for drug infusions was observed. Similar data were obtained in rats that were exposed to graded unit doses of heroin (Dai et al., 1989). In general, data from both rats and monkeys revealed that the relationship between log unit dose of a drug and the self-administration rate seems to be an inverted U-shaped curve (Harrigan and Downs, 1978a; Young et al., 1981; Collins et al., 1984; Balster and Lukas, 1985; Lukas et al., 1986; Vaupel et al., 1986; Martin et al., 1997). The decrease in responding with higher doses of the drug might be explained by a cumulative effect of increased reinforcement per infusion, which diminishes the drive of the animal to respond for morphine, and by catalepsy, gnawing, sedation, and satiation. Taken into account the linear function between the log unit dose and drug intake, it seems that the amount of drug intake is a more informative index for the reinforcing efficacy of opioids and of other abused drugs than the number of self-injections (Van Ree et al., 1978). The rate of opioid intake seems not only dependent on the unit dose available for self-administration, but upon the training dose as well. Martin et al. (1998) demonstrated that doses of heroin lower than 5.4 μg/inf maintained higher rates of drug intake in rats trained with 5.4 μg/inf as compared to rats trained with 18 μg/inf heroin, whereas doses higher than 5.4 μg/inf maintained similar rates of heroin intake in both groups of animals.

The various opioids differ markedly in their potencies, i.e., in the unit doses that maintain maximum rates of responding under similar conditions. Comparison of the log dose-response curves of heroin, morphine, methadone, and LAAM in rhesus monkeys showed that all opioids maintained comparable peak self-administration rates, but at different unit doses (Harrigan and Downs, 1978a). The rank order of the relative potency was heroin > LAAM > morphine > methadone (1, 4, 10, and 16 μg/kg/ inf, respectively). Systematic studies with several opioid agonists and mixed opioid agonist-antagonists in different species reveal that under identical access conditions the relative potencies of the different opioid drugs can vary by more than 10,000-fold when taking the peak of the inverted U-shaped dose-response (self-administration rate) as assessment (Young et al., 1981; Collins et al., 1984; Balster and Lukas, 1985; Lukas et al., 1986; Vaupel et al., 1986; Martin et al., 1997).

Another method to estimate the relative potencies of different opioids is to compare their ED_{50} values (i.e., the unit dose of a drug that initiates and maintains reliable self-administration behavior above saline level in 50% of the animals). By offering various unit dose levels of morphine, fentanyl, and heroin, a substantial portion of the animals readily initiated self-administration behavior according to a linear dose-response curve (Van Ree et al., 1978). The calculated relative ED_{50}

values were 2.5 μg/kg/inf for fentanyl, 50 μg/kg/inf for heroin, and 650 μg/kg/inf for morphine. Interestingly, comparison of the reinforcing and analgesic properties of these opioids revealed an accurate similarity between the relative ED_{50} values for self-administration behavior and the relative potencies of these drugs for analgesia.

The dose of a drug is also an important determinant of the temporal distribution of opioid self-injections (Van Ree et al., 1978; Weeks and Collins, 1979). Drug-naive rats offered 10 mg/kg/inf morphine under a continuous reinforcement schedule seldom took more than one injection at the time. When the dose of the drug is reduced to 3.2 mg/kg/inf, double and an occasional triple injections were seen. With much smaller doses (32 μg/kg/inf), rats usually take morphine in series of closely spaced injections (up to 50 injections), and then a pause with only sporadic injections until the next series (Weeks and Collins, 1979). Looking at the interinfusion intervals, a higher percentage of relatively low interinfusion intervals (1–10 min) was found when a low dose of morphine, heroin, or fentanyl was offered, whereas longer intervals (30–60 min) between infusions occurred more frequently when the unit dose per injection was higher (Van Ree et al., 1978).

In conclusion, the unit dose of a drug delivered is one of the main factors which determines the ultimate level of drug intake during self-administration. The amount of drug taken can serve as a useful index of the reinforcing efficacy for the reinforcer (i.e., drug injection).

2. Route of Administration. Opioids can be self-administered via a wide range of routes, i.e., p.o., i.v., i.p., s.c., intragastric, i.c.v., or intracerebral (Smith et al., 1976; Jones and Prada, 1977; Carroll and Meisch, 1978; Van Ree and Niesink, 1978; Van Ree and De Wied, 1980; Bozarth and Wise, 1981b; Goeders et al., 1984; France et al., 1985). Intracerbroventricular and intracerebral administration will be discussed later (see *III. Central Sites of Action*). One of the difficulties encountered with the oral self-administration procedure is the aversive taste of some opioid drugs. For example, morphine in solution is a weak base with a bitter taste that laboratory animals often do not accept. Nonetheless, several studies have demonstrated reliable oral morphine self-administration in rats (Cappell and LeBlanc, 1971; Leander et al., 1975; Van Ree and Niesink, 1978). Etonitazene, a potent opioid, appeared to have little if any taste and served as a positive reinforcer orally in rats and rhesus monkeys (Wikler et al., 1963; McMillan and Leander, 1976; Meisch and Stark, 1977; Carroll and Meisch, 1978; Heyne, 1996).

The total intake of a drug depends on the route of administration and the speed at which the drug reaches the brain, in the sense that the reinforcing effects increase as the concentration of the drug at the site of action increases. For example, drug-naive rats offered a wide dose range of morphine via an i.v. route showed

self-administration behavior according to the unit dose delivered, with a maximum number of self-infusions at a unit dose of 30 μg/kg/inf (Fig. 1) (Smith et al., 1976). In rats offered morphine via an intragastric route, a unit dose of 30 μg/kg/inf morphine did not maintain responding. The curve of intragastric morphine reinforcement was shifted to the right and the maximum number of self-infusions was lower than with the i.v. route (maximum number of self-infusions at 300 μg/kg/inf). These data indicate that the i.v. route enables a more potent (and efficacious) behavioral effect of morphine. Placement of the drug directly into the blood as compared with oral delivery enables a higher quantity of the agent at its site of action with a more rapid onset, which probably increases the drugs' reinforcing effects. Administration of morphine via the intragastric route might cause loss of potential through incomplete and slow absorption, biotransformation, and delayed latency of onset (Iwamoto and Klaassen, 1977).

3. Schedules of Reinforcement. Schedules of reinforcement or schedules of drug availability can influence opioid self-administration behavior in animals. The schedules used include fixed ratio (FR) schedules where a fixed number of behavioral responses is required to obtain a drug, and fixed interval schedules where the drug can be obtained after a fixed amount of time responding for it. Studies with these schedules of drug availability generally show that an increase in response requirement or interinjection interval decreases the amount of drug self-administered. In general, the influence of the various schedules of reinforcement on drug self-administration is comparable to that on food and water reinforcement.

A typical model of schedule-controlled responding is the progressive-ratio paradigm. This model, in which each next drug infusion requires more responses than the one before (increased FR requirement), allows the determination of the maximal effort the animal will perform to receive a drug infusion ("breaking point"). The breaking point depends on the dose of the self-administered drug and is thought to provide a measure of the reinforcing efficacy of the drug. For example, Hoffmeister (1979) investigated the reinforcing efficacy of a number of opioid drugs in rhesus monkeys using a day-by-day increasing progressive ratio schedule. Before opioid drug experiments, stable self-administration behavior was established with 1-mg/kg codeine infusions contingent on completion of a FR 100. Doses of the opioid drug studied were substituted for codeine and the FR schedules were doubled daily (up to FR 64,000) until the number of self-infusions per day decreased to less then two infusions (the breaking point). The breaking points of either opioid drug studied, i.e., heroin, codeine, dextropropoxyphene, and pentazocine, increased dose-dependently. The highest breaking point with heroin (FR 12,800) was observed with infusions of 0.5 mg/kg and for codeine (FR 6,400) with a dose of 16 mg/kg/inf.

When dextropropoxyphene and pentazocine maintained behavior, the highest breaking points (FR 6,400) were observed with infusions of 5 mg/kg. The progressive ratio paradigm demonstrates a certain rank ordering in the breaking points, i.e., the reinforcing efficacy, of different opioid drugs. It has been argued that the progressive ratio model provides a measure of drug craving in the presence of the drug (Markou et al., 1993). The authors emphasize that the breaking point measure is composed of two components: the unconditioned incentive (i.e., reinforcing) and the conditioned incentive properties of the drug. According to this, the fact that animals will exhibit more effort to receive one of two unit doses can be considered to reflect the relative incentive motivational value of the expected drug dose, and thus a measure of drug craving.

Another schedule-controlled paradigm, which also is thought to provide a measure for drug craving, is the second-order schedule paradigm (Markou et al., 1993). A second-order schedule is defined as "one in which the behavior specified by a schedule contingency is treated as unitary response that is itself reinforced according to some schedule of primary reinforcement" (Kelleher, 1966; Goldberg and Gardner, 1981). In short, completion of a specific FR schedule results in the presentation of a brief stimulus and completion of an overall schedule produces a brief stimulus and a drug injection. For example, every 30th key-pressing response during a 60-min interval produced a 2-s light; the first 30-response component completed after 60 min produced both the light and an i.v. injection with morphine (Goldberg and Tang, 1977). Under this second-order schedule of morphine injections, high rates of responding were maintained by monkeys and the unit dose-response relationship tends to be an inverted U-shaped curve. The second-order schedule can be repeated several times which will result in multiple drug injections. One of the advantages of second-order schedules as a model for drug craving is that animals will perform a high rate of responding and extended sequences of behavior before any drug administration.

4. Physical Dependence, Tolerance, and Sensitization. Repeated self-administration of drugs may alter a variety of homeostatic mechanisms, changes that alternatively may contribute more or less to drug-taking behavior. The development of physical dependence and tolerance is of particular interest, since these phenomena have been regarded in the past as being critically involved in opioid addiction.

Physical dependence refers to an altered physiological state produced by the repeated administration of a drug, which necessitates the continued administration of the drug to prevent the appearance of a withdrawal or abstinence syndrome (Jaffe, 1990). Tolerance represents a decrease in effectiveness of a drug after repeated administration and consequently the need for a higher dose to produce the same effect. Treatment of animals with

opioids to an extent that physical dependence is induced will usually also result in animals tolerant to particular actions of opioids. Thus, the following discussion about physical dependence is also appropriate for opioid tolerance. To investigate the contribution of physical dependence on opioids to i.c.v. heroin self-administration in rats, De Vry et al. (1989b) allowed naive rats to self-administer different doses of heroin (0.125–2 μg/inf) for five daily sessions of 3 h. The rats initiated heroin self-administration, according to an inverted U-shaped dose-response curve, with the 0.5-μg/inf dose inducing the highest infusion rate. The nociceptive response of the animals assessed after the completion of the fourth session did not reveal significant analgesia. A naloxone challenge given immediately after the fifth session induced very mild withdrawal signs only in the group that administered the highest dose of heroin. Thus, physical dependence does not seem a prerequisite for opioid self-administration behavior. Heroin self-administration is apparently initiated and maintained at doses lower than those inducing physical dependence and analgesia. Accordingly, in rats that i.c.v. self-administer morphine, heroin, or β-endorphin, no or only mild withdrawal signs were observed upon naloxone challenge (Amit et al., 1976; Van Ree et al., 1979). Other experimental evidence also indicates that the physical dependence-creating properties of opioids are of minor importance for self-administration behavior. For instance, monkeys will self-administer morphine at doses below those necessary to produce physical dependence (Woods and Schuster, 1968, 1971). Moreover, opioids with weak potential for producing physical dependence (e.g., codeine and methadone) are stronger reinforcers than morphine (Woods and Schuster, 1971). Self-administration of morphine-like mixed opioid agonist-antagonists does not depend on a history of physical dependence (Steinfels et al., 1982; Woods et al., 1982). The amount of heroin i.v. self-administered in rats was not influenced by prior forced injections with heroin, leading to a high degree of physical dependence (Van Ree et al., 1978). Accordingly, the relationship between the unit dose delivered and the amount of drug intake was hardly affected by physical dependence (Dai et al., 1989). When a low unit dose of heroin (30 μg/kg/inf) was offered, the rats showed a higher rate of self-injections when they were physically dependent on heroin as compared to heroin-naive rats. Although this may indicate a role of tolerance in modulating the rate of opioid self-administration, it is by no means clear that tolerance has developed toward the reinforcing effects of opioids, particularly since the effect was observed with the indicated low unit dose only. Moreover, the observed increase in responding may be more related to the development of tolerance to the rate-decreasing properties of the drug (Woods and Schuster, 1971).

When morphine administration is discontinued, by substituting saline for morphine, an initial increase in operant responding is observed followed by a decreased rate of responding (i.e., extinction). This extinction pattern is thought to be dependent on the unit dose of the drug. That is, when a high dose of morphine, which produces recognizable signs of withdrawal upon cessation, is offered during self-administration, an increased responding is observed during initial extinction and the length of extinction is longer. If a low dose of morphine, devoid of physical dependence-producing properties, was offered, the initial increase in responding was absent during extinction (Woods and Schuster, 1971). It was concluded that the transitory increase in responding during the initial extinction could be a result of the development of physical dependence (Woods and Schuster, 1971). However, other studies do not support the hypothesis that the pattern and time of extinction can be used as a measurement of physical dependence. For example, the extinction of rats self-administering fentanyl was significantly slower than that of rats self-administering morphine in doses equipotent for self-administration based on the ED_{50} measure (Van Ree et al., 1974). It was suggested that, beside the dose of the drug, the length of extinction is more dependent on the time between operant responding and the actual reinforcement, which, in turn, is dependent on the speed at which the drug reaches its site of action in the brain. The shorter the time between operant responding (e.g., pressing a lever) and arrival of the drug at its site of action in the brain, the stronger the reinforcing efficacy of the drug. Increased reinforcement then leads to slower extinction. Thus, fentanyl more rapidly penetrates the brain than morphine and consequently, through stronger reinforcement, leads to slower extinction upon saline substitution.

Thus, experimental evidence does not support an important role of both tolerance development toward the reinforcing effects of opioids and of physical dependence for opioid self-administration behavior. It should, however, be kept in mind that tolerance toward other effects of opioids (e.g., depression of motor behavior) could influence self-administration behavior.

A substantial body of evidence suggests that repeated administration of drugs might also produce an effect opposite to tolerance: sensitization. That is, repeated exposure may increase or intensify the effectiveness of a drug. However, limited data are available with regard to sensitization to the reinforcing effects of opioids using the self-administration paradigm. A period of heroin self-administration has been shown to cause a long-lasting enhancement in the sensitivity to the locomotor effects of heroin (De Vries et al., 1998). Pretreatment with morphine, 4 weeks before acquisition of self-administration, enhanced i.c.v. morphine self-administration (Greksch et al., 1998). Preexposure to opioids has also been found to sensitize their effects in the conditioned place preference paradigm (see *V. Tolerance, Physical Dependence, and Sensitization*).

5. Predisposing Variables. a. PRENATAL EXPOSURE. Preexposure to opioids during gestation has a significant effect on the development of drug self-administration in rats. Chronic treatment of female Sprague-Dawley rats with methadone throughout gestation and lactation resulted in an increase in oral self-administration of morphine by their 11- to 12-week-old offspring (Hovious and Peters, 1985). Surprisingly, methadone self-administration in the methadone offspring was not different from controls. Ramsey et al. (1993) showed that 10- to 12-week-old male Wistar rats born from females treated with morphine during gestation exhibited higher heroin intake during initiation of self-administration than their prenatal saline-treated controls. Interestingly, in similarly treated rats initiation of cocaine self-administration was also higher than in the controls. These results suggest that prenatal exposure to opioids may facilitate the development of drug self-administration, hence, being an important risk factor in the etiology of drug addiction.

b. ENVIRONMENTAL FACTORS. Specific environmental factors play a role in the individual differences in drug self-administration. For instance, the effect of manipulation of the social housing conditions on oral morphine self-administration in rats has been examined and it was found that isolation, as compared to group housing, enhanced this behavior (Alexander et al., 1978).

Another environmental factor which might be of significance to drug intake is stress. Nonphysical (emotional) stress as opposed to physical stress (inescapable shocks) and to control conditions enhanced the initiation of i.v. self-administration of morphine in two inbred strains of mice (Kuzmin et al., 1996c). In these experiments, the physical stress consisted of a session of 10 mild unpredictable and inescapable footshocks, and emotional stress meant being forced to witness this treatment. Under similar conditions, it has been shown that emotional stress, but not physical stress, enhanced the initiation of cocaine intake in drug-naive rats (Ramsey and Van Ree, 1993). Other experiments have shown that immobilization stress and particularly predictable, repeated footshock stress facilitated oral self-administration of morphine and fentanyl and i.v. self-administration of heroin in rats (Shaham et al., 1992; Shaham and Stewart, 1994; Klein et al., 1997). Together, it can be concluded that stress, and in particular emotional distress, might increase the development of opioid self-administration.

The nutritional state of a subject can also interfere with the reinforcing effects of the drug. It has been demonstrated that food restriction increased drug-reinforced behavior and drug intake. This deprivation-induced facilitation was found with most classes of drugs, including opioids, during maintenance as well as during initiation of drug self-administration (Takahashi et al., 1978; Caroll et al., 1981; Oei, 1983; De Vry et al., 1989a). It has been hypothesised that body weight reduction, and not food deprivation per se, gives rise to differential sensitivity to the reinforcing properties of the drugs (Oei, 1983; Carroll and Meisch, 1984). The increased drug self-administration may probably result from an interaction between weight loss-induced general activity and weight loss-induced sensitization to the reinforcing effects of the drug (De Vry et al., 1989a). In addition, it has been shown that the presence of a fixed time, noncontingent food delivery schedule facilitated the rate of acquisition of heroin self-administration (Oei et al., 1980; Wallace and Van Ree, 1981).

c. GENETIC FACTORS. The possible role of genetic factors in drug dependence has received increasing attention over the last years. Sophisticated animal models have been developed to investigate the contribution of genetic factors in the individual sensitivity for the reinforcing effects of drugs of abuse. These models range from selective breeding of animals with characteristic responding for drugs to the construction of recombinant inbred strains (Crabbe and Belknap, 1992). Over the years much effort has been put in the selection and breeding of genetically different strains of animals responding for alcohol (George, 1993). Fewer attempts have been made to genetically select animals on the basis of their sensitivity for other drugs of abuse, although several groups have reported on genetic differences in opioid intake. Differences in intake of the pure opioid agonists morphine or etonitazine have been found in different rat stocks (Carroll et al., 1986b), selectively bred rat strains (Satinder, 1977), inbred rats (Suzuki et al., 1992a; Ambrosio et al., 1995), and inbred mice (Horowitz et al., 1977; Kuzmin et al., 1996c). As an example, initiation of i.v. morphine self-administration was tested in two genetically inbred strains of mice (C57BL/6 and DBA/2) (Kuzmin et al., 1996c). It was found that whereas DBA/2 readily initiated morphine self-administration according to an inverted U-shaped dose-response curve, the C57BL/6 mice did not initiate morphine intake. However, exposure to acute emotional stress induced by forcing mice to witness another mouse receiving footshocks caused the C57BL/6 mice to start self-administering morphine. Furthermore, as with psychostimulants, a relationship has been proposed between high locomotor response to a novel environment and a high morphine intake during initiation of self-administration (Ambrosio et al., 1995; Piazza and Le Moal, 1996). Rats with a high preference for saccharin showed more morphine self-administration than rats with a low preference for saccharin (Gosnell et al., 1995). The primary importance of these kind of studies is that they indicate that genotype can be a specific determinant of drug-taking behavior. Moreover, the study of Kuzmin et al. (1996c) reveals that genetic and environmental factors interact in the sensitivity for opioid reinforcement.

6. Treatment Interference Studies. The drug self-administration model has been used to evaluate possible new pharmacotherapies for the treatment of opioid addic-

tion. Mixed opioid agonists-antagonists influence opioid self-administration behavior. Buprenorphine, a mixed opioid agonist-antagonist with lower efficacy than morphine for the μ receptor (Reisine and Pasternak, 1996; Holtzman, 1997), suppressed opioid self-administration in primate models. Long term treatment with buprenorphine (i.v.) suppressed i.v. heroin and hydromorphone self-administration and decreased the intake of alfentanil in monkeys (Mello et al., 1983; Winger et al., 1992). Nalbuphine, another mixed opioid agonist-antagonist, produced similar reductions in i.v. alfentanil self-administration. Cyclazocine, a μ antagonist/κ agonist, prevented self-administration of morphine in rats (Archer et al., 1996). Studies in humans have shown that the mixed opioid agonists-antagonists nalbuphine and dezocine produced opioid antagonistic effects in opioid-dependent subjects, i.e., precipitating a withdrawal syndrome only slightly different from that produced by naloxone (Preston et al., 1989; Strain et al., 1996a). Buprenorphine, on the other hand, seems to be a potentially effective pharmacotherapy for opioid addiction (e.g., Johnson et al., 1995b; Mendelson et al., 1996; Strain et al., 1996b), although the potential abuse liability of buprenorphine may compromise its development of treatment for drug addiction (O'Connor et al., 1988; Chowdhurry and Chowdhurry, 1990; Mendelson et al., 1997).

Neuropeptides related to hypothalamic-neurohypophyseal hormones also affect i.v. opioid self-administration. Daily s.c., oral, or i.c.v. treatment with desglycinamide^9-[Arg^8]-vasopressin (DG-AVP) decreased heroin intake during initiation of self-administration behavior (Van Ree and De Wied, 1977a,b; Van Ree, 1980, 1982; Van Ree et al., 1988). Fentanyl self-administration directly into the ventral tegmental area (VTA) was also decreased by s.c. treatment with DG-AVP, suggesting that the interaction between DG-AVP and opioid reinforcement is located in the VTA, which is supported by the decreasing effect of DG-AVP on ICSS from this area (Dorsa and Van Ree, 1979; Van Ree and De Wied, 1980). The effect of DG-AVP may be particularly effective during the development of opioid self-administration behavior (Van Ree, 1982). Accordingly, DG-AVP did not reduce morphine self-administration in well trained monkeys physically dependent on morphine and with a long history of self-administration (Mello and Mendelson, 1979). Vasopressin neuropeptides may be physiologically involved in heroin self-administration, since removal of vasopressin by injecting vasopressin antiserum directly into the cerebrospinal fluid led to facilitation of self-administration behavior (Van Ree and De Wied, 1977a). In some limited studies with DG-AVP in heroin addicts on ambulant methadone-detoxification, it was found that administration of DG-AVP sublingually during the initial phase of methadone detoxification facilitated the detoxification of heroin addicts and decreased heroin and cocaine intake (Van Beek-Verbeek et al., 1979, 1983; Van Ree, 1980; Fraenkel et al., 1983). Accordingly, s.c. treatment with DG-AVP decreased initiation of i.v. cocaine self-administration behavior in rats (De Vry et al., 1988; Van Ree et al., 1988). Interestingly, neuropeptides related to the other neurohypophyseal hormone, i.e., oxytocin, had an effect opposite to that of vasopressin, since i.v. heroin and intra-VTA fentanyl self-administration behavior and ICSS from the VTA were facilitated after treatment with the C-terminal tripeptide of oxytocin, prolyl-leucyl-glycinamide (Van Ree and De Wied, 1977b, 1980; Dorsa and Van Ree, 1979.

Other neuropeptides have also been tested for modulation of i.v. opioid self-administration. Although s.c. treatment with the opioid β-endorphin [β-endorphin-(1–31)] hardly affected initiation of heroin self-administration, the neurolepticum-like peptides β-endorphin-(2–17) and β-endorphin-(6–17) (γ-endorphin-related peptides) decreased and the psychostimulant-like peptide β-endorphin-(2–9) (α-endorphin-related peptide) slightly increased heroin intake (De Wied et al., 1978; Van Ree, 1979; Van Ree and De Wied, 1982a; Van Ree and De Wied, 1982b; Van Ree, 1983). Accordingly, similar modulatory effects of these neuropeptides have been reported for ICSS from the ventral tegmental-substantia nigra area (Dorsa et al., 1979). γ$_2$-melanocyte-stimulating hormone, which behavioral profile resembles that of naloxone in several aspects decreased heroin intake during initation of self-administration (Van Ree et al., 1981; Van Ree, 1983). The cholocystokinine type A receptor antagonist devazepine did not alter i.v. heroin self-administration in trained rats (Higgins et al., 1994a).

Serotonin (5-hydroxytryptamine, 5-HT) systems have been implicated in opioid self-administration. Zemilidine, a 5-HT uptake inhibitor, dose-dependently reduced the oral morphine consumption by opioid-dependent rats (Rockman et al., 1980; Ronnback et al., 1984). Fluvoxamine, a 5-HT uptake inhibitor, and ipsapirone, a 5HT$_{1A}$ agonist, when given during existing oral morphine consumption, increased morphine intake, whereas ipsapirone, when given before exposure to morphine, increased subsequent oral morphine intake (Mosner et al., 1997). Systemic treatment with the 5-HT releaser/reuptake inhibitor, dexfenfluramine, transiently reduced i.v. heroin self-administration in rats, an effect that was antagonized by simultaneous treatment with the 5-HT$_{1/2}$ antagonist metergoline, the 5-HT$_2$ antagonist ritanserin, but not with the 5-HT$_3$ antagonist ondansetron and the peripherally acting 5-HT antagonist xylamidine (Higgins et al., 1993, 1994b; Wang et al., 1995). Finally, lesioning the serotonergic innervations of the nucleus accumbens (NAC), by bilateral injection of 5,7-dihydroxytryptamine into this area, resulted in an increase of i.v. morphine self-administration in rats made physically dependent on morphine (Smith et al., 1987; Dworkin et al., 1988b). Although brain serotonergic systems seem to play a role in opioid self-administration, more experimentation is needed before definite conclusions can be drawn.

Investigations of a cholinergic influence on opioid self-administration revealed a suppressive effect of the

cholinergic antagonist atropine on i.v. morphine self-administration in rats (Davis and Smith, 1975; Glick and Cox, 1975). Self-administration of morphine was accompanied by an increased acetylcholine turnover rate in limbic regions (Smith et al., 1980, 1984).

Treatment with the DA-β-hydroxylase inhibitors, diethyldithiocarbamate, U-14,624, or FLA-57, suppressed the voluntary ingestion of morphine and prevented the reacquisition of i.v. morphine self-administration in rats (Davis et al., 1975; Brown et al., 1978). These treatments produced a concomitant reduction in central norepinephrine levels.

Using a 1-day i.v. self-administration procedure in drug-naive mice, it was demonstrated that s.c. treatment with the dihydropyridine calcium channel antagonists isradipine and nimodipine, and the agonist BayK 8644, decreased and increased, respectively, i.v. morphine self-administration (Kuzmin et al., 1992b, 1994, 1996a). It was suggested that the inhibition of the reinforcing properties of morphine (and cocaine) is due to the ability of the calcium antagonists to block L-type calcium channels, thereby affecting the turnover or release of neurotransmitters (Martellotta et al., 1994; Kuzmin et al., 1996b).

Systemic ibogaine, a naturally occurring indole alkaloid, produced an acute dose-dependent depression of i.v. opioid self-administration in rats. Although this action may be due to decreasing the reinforcing properties of opioids, it may also be related to the acute nonspecific side effects of ibogaine (e.g., tremors, decreased motivated behavior) interfering with lever-pressing (Glick et al., 1991; Dworkin et al., 1995). A day after ibogaine administration the rates of opioid self-administration were still significantly decreased, although others disagree (Glick et al., 1991; Dworkin et al., 1995). This "aftereffect" of ibogaine on opioid intake has been suggested to result from some persistent modulatory action of ibogaine on the reinforcing efficacy of opioids, possibly mediated by noribogaine, a metabolite of ibogaine (Glick et al., 1996b). Glick et al. (1994) investigated whether other iboga alkaloids, as well as chemically related harmala alkaloids, would reduce morphine self-administration. Although all tested alkaloids dose dependently decreased morphine intake acutely after treatment, only some alkaloids (i.e., ibogaine, tabernanthine, desethylcoronaridine, and the R-isomers of coronaridine and ibogamine) still decreased morphine intake a day after administration. Similarly, 18-methoxycoronaridine, a synthetic iboga alkaloid congener without ibogaine's adverse tremorigenic and neurotoxic side effects, was found to produce acute and long-lasting decreases in morphine self-administration (Glick et al., 1996a). The effects of ibogaine may be related to modulation of the N-methyl-D-aspartate (NMDA) receptor complex (Popik et al., 1994, 1995).

C. Endogenous Opioids and Opioid Drugs of Abuse

1. Opioid Receptor Types. Mediation of the reinforcing effects of opioids through activation of opioid receptors has been demonstrated by several studies using opioid antagonists (for review, see Mello and Negus, 1996). Intravenous morphine self-administration by rats and monkeys was attenuated by systemic administration of the opioid antagonists naloxone, naltrexone, and nalorphine (Goldberg et al., 1971; Weeks and Collins, 1976; Harrigan and Downs, 1978b). Opioid receptor blockade by naloxone or naltrexone produced dose-dependent increases in i.v. self-administration of heroin in rats, an effect, which was interpreted as a compensation for the reduced reinforcing effects of heroin (Ettenberg et al., 1982; Koob et al., 1984). Higher doses of these drugs produced transient decreases in self-administration, followed by recovery. i.v. opioid self-administration in rats was found to be particularly sensitive for the effects of naltrexone, since significant alterations in heroin intake were observed at doses as low as 0.05 and 0.1 mg/kg. (Koob et al., 1984).

Using antagonists selective for μ-, δ- and κ-opioid receptors as well as the μ_1-receptor antagonist nalozonazine, Negus et al. (1993) showed that in particular the μ-opioid receptor plays an important role in the reinforcing effects of heroin in rats. They found that pretreatment with the μ-opioid receptor antagonist β-funaltrexamine produced a significant increase in heroin intake, whereas some doses produced an extinction-like pattern of responding. These results were quantitatively similar to the effects of lowering the unit dose of heroin per injection. In another study, it was shown that i.c.v. administration of β-funaltrexamine decreased heroin self-administration for a number of days (Martin et al., 1995). Pretreatment with the δ-opioid receptor antagonist naltrindole also produced a significant increase in heroin intake, but no extinction-like pattern suggesting that the δ-opioid receptors might also be involved in opioid reinforcement, albeit less pronounced. The κ-opioid receptor antagonist nor-binaltorphimine (nor-BNI) modestly decreased heroin self-administration in one study (Xi et al., 1998), but failed to affect heroin self-administration in another study (Negus et al., 1993). Different groups have reported an effect of stimulation of the κ-opioid receptor on opioid self-administration. Two κ-opioid agonists, U50,488H and spiradoline, produced dose-related extinction-like decreases in morphine self-administration for several days in rats (Glick et al., 1995). Pretreatment with the κ-opioid antagonist nor-BNI had no effect on morphine intake itself, but fully antagonized the effects of U50,488H. Furthermore, modulation of the reinforcing effects of morphine by κ-opioid receptor stimulation in drug-naive mice was studied (Kuzmin et al., 1997b). Treatment with the κ-agonist U50,488H dose-dependently decreased the intake of morphine when offered in unit doses that readily initiated self-administration behavior. In addition, treatment with U50,488H induced proper self-

administration behavior with lower, subthreshold unit doses of morphine. It was found that activation of the κ-opioid receptor with U50,488H produced an almost parallel shift to the left in the inverted U-shaped dose-response curve for morphine self-injection rates, indicating an increased sensitivity of the animals for the reinforcing effects of morphine. Similar effects were observed with cocaine self-administration in rats (Kuzmin et al., 1997b). Xi et al. (1998) reported that administration of a low dose of the κ-opioid agonist U50,488H significantly increased heroin self-administration in rats, whereas a high dose of U50,488H blocked heroin intake.

The involvement of the μ-opioid receptor for opioid reinforcement has also been demonstrated using an inbred mouse strain with a low number of μ-opioid receptors in the central nervous system (Elmer et al., 1995). In these mice, opioid reinforced behavior was determined using oral self-administration behavior of the opioid agonist etonitazine. Initiation of this behavior was readily established, but differences were present during the maintenance phase and during extinction of self-administration. Mice with more μ-opioid receptors showed a significant enhancement in the efficacy of morphine to act as reinforcer (Elmer et al., 1996).

2. Central Sites of Action. The finding that animals self-administer morphine and heroin into the ventricle (Amit et al., 1976; Stein and Belluzzi, 1978; Van Ree et al., 1979) strongly suggests that central loci subserve the reinforcing effects of opioids. Furthermore, the lack of effect of opioid antagonists which are not able to pass the blood-brain barrier (i.e., quaternary opioid antagonists) on opioid self-administration supports the involvement of central opioid systems in opioid reinforcement (Koob et al., 1984; Vaccarino et al., 1985b). To localize the central site of the reinforcing action of opioids, two procedures are typically applied. One procedure is intracranial opioid self-administration. In short, naive rats are stereotaxically prepared with guide cannulas aimed just above an area of interest and are allowed to self-administer morphine into this area over several consecutive sessions by pressing a lever. The second procedure is investigating the effects of localized opioid antagonist injections into discrete brain regions on i.v. opioid self-administration.

In a first attempt to determine which areas within the CNS are involved in opioid reinforcement Stein and colleagues, using the intracranial self-administration technique, demonstrated high rates of morphine self-administration into the lateral hypothalamus, amygdala and preoptic area (Stein and Olds, 1977; Stein and Zirneskie, 1979). Considerably lower rates were found in the central gray and the septum. Inactive regions, i.e., regions not maintaining significant lever-pressing, included the lateral thalamus, nucleus caudatus, cortex, cerebellum, and reticular formation. On the basis of, among others, these early reports, Olds (1979) further explored the involvement of the lateral hypothalamus

(LH) in opioid reinforcement. During 22-h sessions rats were offered either morphine or vehicle. A dose of 0.2 μg/inf morphine, but not 0.1 μg/inf, produced a significantly higher rate of self-administration behavior as compared with animals offered vehicle. Moreover, some of the animals learned successfully to reverse repeatedly when the active lever delivering morphine was changed from one side of the test chamber to the other in successive sessions. Intrahypothalamical administration of a mixture of morphine with the opioid antagonist, naloxone (0.02– 0.04 μg/inf) reduced or completely abolished self-administration, suggesting that the reinforcing effects of morphine are mediated through opioid receptors in the hypothalamus. About 20 years later Cazala and colleagues, using a spatial discrimination test in a Y-maze, attempted to determine whether mice will self-administer morphine into the LH (Cazala et al., 1987; Cazala, 1990). They demonstrated that when naive mice had access to low doses of morphine (5–50 ng/inf), they rapidly discriminated the reinforced arm from the neutral arm of the maze to self-administer the drug into the LH. When naloxone (5 ng/inf) was mixed with morphine (5 ng/inf), the number of self-injections rapidly decreased. The involvement of opioid receptors in the LH in opioid reinforcement was also examined by means of intracranial injections of opioid antagonists. Microinfusions of methylnaltrexone (1.0 and 3.0 μg) into the LH produced significant dose-related increases in responses for heroin infusions in animals trained to i.v. self-administer low doses of heroin (Corrigall, 1987). This change in response is considered to reflect a compensatory increase in responding due to a decrease in the reinforcing effects of heroin.

Another brain area, which has been investigated for a role in opioid reinforcement, is the VTA. Several studies showed that naive rats rapidly learned to lever-press or nose-poke for microinfusions of low doses of morphine (50 and 100 ng/inf) directly into the VTA, an action which could be effectively blocked by systemic administration of an opioid antagonist (Bozarth and Wise, 1981b; Welzl et al., 1989; Devine and Wise, 1994). Naive rats also lever-pressed for infusions of the opioid agonist fentanyl (2.5 ng/inf) into the VTA (Van Ree and De Wied, 1980). Opioid blockade in the VTA with the quaternary opioid antagonists diallyl-normorphinium and methyl-naloxonium significantly attenuated i.v. heroin self-administration (Britt and Wise, 1983; Vaccarino et al., 1985a), suggesting an involvement of VTA opioid receptors in opioid reinforcement, although the antagonistic action of diallyl-normorphinium is questionable (Valentino et al., 1983). In mice, morphine self-administration (5 and 50 ng/inf) into both the VTA and the amygdala was observed. Interestingly, a preference for self-injection into the VTA was found in animals given the opportunity to choose between the two sites (David and Cazala, 1994, 1998). Using the reinstatement model, it was found that morphine injected into the VTA, but not

in the nucleus caudatus and periventricular gray, could reinstate lever-pressing, previously resulting in i.v. heroin or cocaine injections. This priming effect of morphine was attenuated by prior administration o f naltrexone (Stewart, 1984; Stewart et al., 1984).

Intracranial self-administration studies also suggest that opioid systems in the NAC may be part of the structures mediating the reinforcing effects of opioids. Olds (1982) demonstrated that self-administration was induced and maintained by morphine infusions (0.2 μg/inf) into the NAC and blocked by coadministration of naloxone. Bozarth (1983), however, was not able to establish a self-administration behavior of a similar dose of morphine in this area. Based on the divergent findings with respect to the involvement of the NAC in opioid reinforcement, studies examining the effects of intra-NAC administration of different quaternary opioid antagonists on heroin self-administration were performed. However, the results from these studies also seem controversial. Britt and Wise (1983) did not find an effect of intra-NAC infusions with the antagonist diallyl-normorphinium on the rate of i.v. heroin self-administration, whereas others demonstrated that infusions with a low dose of methylnaloxonium into the NAC significantly attenuated i.v. heroin self-administration (Vaccarino et al., 1985a; Corrigall and Vaccarino, 1988). The discrepancy between the results of these studies might be explained by the fact that diallyl-normorphinium, unlike methylnaloxonium, has been shown to be ineffective as an opioid antagonist in commonly used bioassays for opioids and seems to have opioid agonistic properties as well (Valentino et al., 1983). That the NAC may be involved in opioid self-administration was also suggested from data showing that kainic acid-induced lesion of the cell bodies of the NAC disrupted i.v. heroin and morphine self-administration (Zito et al., 1985). Moreover, inactivation of G_i and G_0 by injecting pertussis toxin in the NAC resulted in a long-lasting increase in i.v. heroin self-administration (Self et al., 1994; Self and Nestler, 1995).

Some studies were aimed at a possible role of the periaquaductal gray (PAG) in mediation of opioid reinforcement. Intracranial self-administration studies showed that morphine self-administration into the PAG could not be established in opioid-naive rats (Bozarth, 1983). However, rats made physically dependent on morphine by continuous intra-PAG infusion of morphine for 72 h readily learned to self-administer 0.1-μg infusions of morphine into the PAG (Bozarth and Wise, 1984). In a study using mice it was, however, shown that a low dose of morphine (5 ng/inf) was readily self-administered into the PAG by opioid-naive animals (Cazala, 1990). Self-administration was more difficult to detect in the opioid-naive mice when a 10 times higher dose of morphine was applied, since the animals rapidly adopted a strategy of delaying the infusions. Based on his findings in mice, Cazala (1990) suggested that the

absence of intra-PAG morphine self-administration in opioid-naive rats (Bozarth, 1983) might originate from the above-mentioned response-inhibiting effects which could be present since a relatively high dose of morphine (100 ng/inf) was offered. Opioid antagonist treatment with methylnaltrexone (1 μg) in the PAG significantly increased heroin intake, suggesting a role of opioid receptors in the PAG in opioid reinforcement (Corrigall and Vaccarino, 1988).

In a study the role of the ventral pallidum, a major projection area of the NAC, in mediation of opioid self-administration has been investigated. That is, lesions of the ventral pallidum reduced heroin self-administration in rats (Hubner and Koob, 1990). Another study suggests an involvement of the pedunculopontine tegmental nucleus in opioid reinforcement, in that lesions of the pedunculopontine tegmental nucleus decreased the responding for heroin infusions during acquisition of this behavior (Olmstead et al., 1998).

Thus, opioid systems in specific areas in the brain are involved in mediation of opioid reinforcement. Moreover, it seems that opioid systems in different brain areas are involved in distinct aspects of opioid actions. For instance, it has been demonstrated that repeated morphine infusions into the VTA did not produce signs of withdrawal in the animal. Morphine self-administration into the PAG and LH produced overt signs of physical dependence (e.g., teeth chattering and wet dog shakes) in animals challenged with naloxone (Bozarth and Wise, 1984; Cazala, 1990). This suggests that opioid systems in the PAG and LH are involved in the physical dependence-creating properties of opioids, whereas opioid systems in the VTA, and possibly the NAC, might be more concerned with the reinforcing effects of opioids.

With regard to the opioid systems in the VTA and NAC, Vaccarino et al. (1985a) performed a study in which they compared the effect of local treatment with the quaternary opioid antagonist methylnaloxonium on i.v. heroin self-administration. They found that the lowest intra-NAC dose of methylnaloxonium needed to increase heroin self-administration was 8 times lower than the dose of the opioid antagonist that attenuated i.v. heroin self-administration when injected into the VTA. The authors suggested that opioid receptors in the NAC play a crucial role in opioid reinforcement, while those in the VTA might be of secondary importance in mediating opioid self-administration. However, i.c. self-administration studies suggest the opposite. Intra-VTA morphine self-administration is maintained by doses of morphine (0.1 μg/inf) (Phillips and LePiane, 1980; Bozarth and Wise, 1981b; Devine and Wise, 1994) that were not able to establish and maintain self-administration behavior in the NAC (Olds, 1982). Moreover, in rats trained to i.v. self-administer heroin, application of morphine centrally in the VTA, but not in the PAG and the nucleus caudatus readily reinstated heroin self-administration (Stewart, 1984). This priming effect

of morphine was attenuated by prior systemic administration of naltrexone.

The involvement of central opioid systems involved in opioid reinforcement has also been studied with i.c.v. and intracerebral self-administration of endogenous opioids. Belluzzi and Stein (1977) first reported that opioid-naive animals will work for enkephalin injections delivered directly in the brain ventricles. They found self-administration of Leu-enkephalin and Met-enkephalin at rates proximately 2 to 4 times higher than those of controls. This finding was confirmed by Smith et al. (1982) , who observed i.c.v. self-administration of Leu-enkephalin in naive animals. Physically dependent animals also maintained self-administration behavior when [D-Ala^2]-Met-enkephalin was substituted for morphine (Tortella and Moreton, 1980). These results indicate that enkephalins may possess positive reinforcing properties similar to morphine through an action in the brain. At the same time, however, other investigators reported that naive animals did not self-administer Met-enkephalin i.c.v., whereas the animals readily self-administered heroin and the endogenous opioid β-endorphin (Van Ree et al., 1979). In addition, i.v. self-administration in rats physically dependent on morphine has been reported for dynorphin-(1–13) and [D-Ala^2]-dynorphin-(1–11) (Khazan et al., 1983).

Goeders et al. (1984) demonstrated that naive rats initiated self-administration of Met-enkephalin, which has affinity for the μ- and δ-opioid receptor, into the NAC. Earlier, other groups reported the self-administration of Met-enkephalin analogs into the LH and the VTA (Olds and Williams, 1980; Phillips and LePiane, 1982). Devine and Wise (1994) evaluated the involvement of μ- and δ-opioid receptors in the VTA in opioid self-administration and showed that morphine, [D-Ala,N-Me-Phe^4,Gly-ol^5]-enkephalin (DAMGO; a selective μ agonist) and [D-Pen^2, D-Pen^5]-enkephalin (DPDPE; a selective δ agonist) effectively established and maintained self-administration into this area. They found that the effective dose of DAMGO was 100 times lower than the effective doses for DPDPE and morphine, suggesting that the major contribution of ventral tegmental mechanisms to opioid self-administration involved an action of μ-opioid receptors. Stevens et al. (1991) demonstrated that rats will lever-press for injections of the opioid dynorphin A directly into the CA3 region of the hippocampus. Coadministration of the opioid antagonist naloxone dose-dependently attenuated this behavior, suggesting that dynorphin reinforcement is regulated through an opioid receptor. The nonselectivity of naloxone probed the investigators to coadminister antagonists selective for μ-, δ-, and κ-opioid receptors. Only blockade of the μ-opioid receptor in the hippocampus completely eliminated the reinforcing effects of dynorphin A, indicating that the μ-opioid receptor in the CA3 region of the hippocampus may be a target site for opioid reinforcement. Together, these data suggest a specific role for μ-opioid receptors present in the VTA and probably some other

areas like the NAC, lateral hypothalamus and hippocampus in opioid reinforcement, although an involvement of δ-opioid receptors can, as yet, not be excluded.

3. Effects on Endogenous Opioid Systems. Opioids have the ability to regulate the activity of the endogenous opioid systems, an action which in turn may be responsible, at least in part, for the reinforcing effects of opioids (for review, see Trujillo et al., 1993). In a clinical study it was found that the plasma levels of β-endorphin immunoreactivity (βE-IR) in heroin addicts were about 3 times lower than that of normal subjects, suggesting that the endorphin system in chronic heroin addicts is depressed (Ho et al., 1979). Experimentally, the regulation of the endorphin system by opioids has been studied in animals. In one of the first reports, it was demonstrated that acute treatment of rats with a high dose of morphine (50 mg/kg i.p.) caused an increase in βE-IR levels in plasma with a concomitant decrease in βE-IR in the anterior lobe of the pituitary and hypothalamus. Chronic treatment with morphine, via pellet implants, decreased βE-IR levels in the pituitary, but did not change the levels of βE-IR in the plasma and hypothalamus (Höllt et al., 1978). Later investigations, using a variety of treatment schedules with opioids, in general supported the finding of a lack of effect on βE-IR levels in the POMC cell body region of the hypothalamus (Przewlocki et al., 1979; Wüster et al., 1980; Berglund et al., 1989; Mocchetti et al., 1989; Bronstein et al., 1990), although one study disagrees (Gudehithlu et al., 1991). With regard to other brain regions, the results are more equivocal. Whereas some studies demonstrated that opioid administration caused a significant decrease in midbrain and septal βE-IR levels, others have found no effect (Przewlocki et al., 1979; Bronstein et al., 1990; Gudehithlu et al., 1991).

To shed more light on the effects of opioids on the activity of the endorphin system, several studies combined the effect of morphine treatment on βE-IR levels and expression of endorphin mRNA (measure for POMC synthesis and processing) in the hypothalamus. Chronic treatment with morphine (3 days of morphine pelleting) did not affect the expression of endorphin mRNA, but significantly increased the levels of βE-IR in the hypothalamus (but see Deyebenes and Pelletier, 1993). Longer morphine treatment (6 days of pelleting), however, caused a significant decrease in the expression of endorphin mRNA in the hypothalamus, without changing the βE-IR levels (Bronstein et al., 1988, 1990; Berglund et al., 1989; Mocchetti et al., 1989). Based on these findings, it was suggested that chronic opioid treatment causes a down-regulation of the endorphin system in the hypothalamus, leading to a decrease in βE synthesis and release. However, the endorphin system seems to compensate over 6 days time in that despite the decreased βE synthesis, no detectable changes in βE-IR levels in the hypothalamus were found.

To investigate the regulation of βE by opioids, Gude-hithlu et al. (1991) undertook a study where they determined the levels of βE-IR in discrete brain regions, pituitary, and plasma in various states of chronic morphine treatment (six morphine pellets in 7 days). They found that in morphine tolerant/physically dependent rats, βE-IR was significantly decreased in the plasma, pituitary, and in restricted brain regions (i.e., the hypothalamus and midbrain). βE-IR levels remained unaltered in the cortex, striatum, hippocampus, amygdala, hindbrain, and spinal cord. During protracted withdrawal from morphine, βE-IR levels were decreased in the pituitary, spinal cord, and amygdala, whereas naloxone-precipitated withdrawal caused βE-IR decreases in the pituitary and hippocampus. Moreover, increases in βE-IR levels were observed in the cortex, midbrain, and hippocampus. The authors concluded that the endorphin system is differentially affected in morphine tolerant/physically dependent and abstinent rats, and that these changes were brain region-specific.

An interesting finding in the potential regulation of βE by opioids is that of Sweep et al. (1988, 1989). They demonstrated that i.v. heroin self-administration for five daily 6-h sessions resulted in a decrease in βE-IR levels in the septum when measured immediately after the fifth self-administration session. At the time of a scheduled next session on day 6, 18 h later, the heroin self-administering animals showed marked decreases in βE-IR in several areas of the anterior limbic system such as the NAC, septum, hippocampus, and rostral striatum. No effects were found in the hypothalamus, thalamus, amygdala, caudal striatum, mesencephalon, or medulla. Interestingly, similar findings were found in animals self-administering cocaine. The authors suggested that the change in levels of β-endorphin and related peptides in these areas might reflect an involvement of endogenous opioids in processes underlying psychic dependence. Moreover, these findings are of particular interest because they address the functional interface between changes in endogenous opioid levels and drug dependence, in contrast to studies wherein drugs are administered by the experimenter.

Several reports have appeared on the opioid regulation of the brain enkephalin system. Although decreases (Przewlocki et al., 1979; Gudehithlu et al., 1991) and increases (Shani and Azov, 1979; Weisman and Zamir, 1987; Tejwani and Rattan, 1997) in enkephalin immunoreactivity in selected brain regions were reported, a majority of studies reported a lack of an effect of opioid treatment on enkephalin immunoreactivity levels in the brain (Childers et al., 1977; Fratta et al., 1977; Wesche et al., 1977; Bianchi et al., 1988; Bronstein et al., 1988; Uhl et al., 1988; Mochetti et al., 1989). Moreover, measuring the enkephalin synthesis in selected brain regions (e.g., hypothalamus and striatum), a lack of effect of several schedules of opioid treatment on enkephalin

mRNA was found (Lightman and Young, 1987; Mochetti et al., 1989; Tjon et al., 1997).

There is increasing evidence that chronic administration of opioids causes significant changes in the dynorphin system in selected brain regions. In short, different schedules of chronic opioid administration (pellets, repeated s.c. injection, chronic i.c.v. infusion) all caused an increase in dynorphin peptides (i.e., dynorphin A, dynorphin B, and α-neo-endorphin) in the brain, predominantly in the dorsal striatum (Weissman and Zamir, 1987; Trujillo and Akil, 1990; Romualdi et al., 1991; Trujillo et al., 1993). At the same time, the expression of dynorphin mRNA was decreased in, among others, the striatum (Romualdi et al., 1989, 1991; Tjon et al., 1997). In a study by Yukhananov et al. (1993) morphine was chronically administered through s.c. implanted osmotic pumps for 5 days. The results showed that the level of dynorphin A (1–17) remained unaltered in several limbic brain regions, including the medial frontal cortex, olfactory tubercle, NAC, and striatum immediately before (morphine-tolerant/physically dependent state) and 20 h after (protracted withdrawal) the pump was removed. During long-term discontinuation from morphine, i.e., after the disappearance of the signs of withdrawal, the level of dynorphin A was, however, significantly lowered in the NAC. Tjon et al. (1997) compared the effects of two different morphine pretreatment regimens on striatal preprodynorphin gene expression. It was observed that an escalating dose regimen (10–50 mg/kg, three daily injections for 5 days), which induced severe physical dependence, caused a transient suppression of dynorphin mRNA expression in caudate putamen and NAC, present 1 day, but not 21 days after cessation of treatment. In contrast, upon repeated intermittent morphine treatment (10 mg/kg, 14 daily injections), a decrease in dynorphin mRNA expression in caudate putamen and NAC was found 1 day, whereas an increase in both regions was observed 21 days post-treatment. From these results it might be suggested that dynorphin particularly participates in mechanisms occurring long after discontinuation of opioid use.

Thus, there seems to be consensus that the endorphin and dynorphin system in different brain areas are affected by opioids. Although the relevance of most of the observed changes for opioid reinforcement is unclear, these endogenous opioids, located in limbic areas, might be involved in psychic dependence and in brain changes occurring long after discontinuation of drug use.

IV. Intracranial Electrical Self-Stimulation

A. Effects of Opioids

The first report about the effect of morphine on ICSS was from Olds and Travis (1960). The self-stimulation behavior was studied over a range of stimulus intensities in animals with electrodes implanted in the lateral hypothalamus (LH), septal area, or VTA. Although it

was found that morphine (7.0 mg/kg i.p.) caused a significant decrease in the response rate in most of the animals, some facilitation of the rate was seen as well. There seemed to be some site specificity of the effects of morphine. Self-stimulation from the VTA was more facilitated by morphine than that from the septal preparations. Conversely, there were more inhibitory effects in the septal than in the tegmental preparations. In most cases, morphine decreased the response rate in animals with electrodes in the hypothalamus.

It lasted about a decade before the next report on this issue was published, probably because of the interest in the procedure of self-administration of morphine and other drugs of abuse as a model to investigate reinforcing properties (Weeks, 1962; Deneau et al., 1969; Van Ree, 1979). In 1972, Adams et al. reported that morphine (10 mg/kg s.c.), decreased self-stimulation behavior in rats with electrodes in the medial forebrain bundle (MFB) during the first 2 h after drug administration. However, thereafter a facilitation of the response rate was observed. Morphine was administered for 5 consecutive days. By day 3, there appeared to be complete tolerance to the inhibitory effect on the response rate along with no tolerance to the facilitating action of morphine. These findings of decreasing and facilitating effects of morphine after acute and repeated administration of the drug has been further analyzed in a number of studies.

Morphine can stimulate and depress motor performance depending upon several variables such as the dose, time between injecting and testing, and presence or absence of tolerance. Since in most ICSS studies a motor response is the measured variable, the effects of morphine on motor performance may interfere with the drug-induced changes in reinforcement, as attempted to measure with ICSS, and may hamper the interpretation of the observed effects. A way to circumvent problems associated with performance changes in rewarded behavior is the determination of the threshold for that behavior. Such a threshold method, usually associated with a low rate of motor performance, may measure reward-induced changes in behavior more accurately and physiologically than methods that are highly dependent on motor performance. Several methods to determine a threshold in operant behavior have been designed (Stein and Ray, 1960; Franklin, 1978; Schaefer and Holtzman, 1979; Ettenberg, 1980). Esposito and Kornetsky (1977) observed a threshold decrease after the administration of morphine in a rate-insensitive "double staircase" psychophysical method to determine threshold of ICSS in rats with electrodes in the MFB. They tested the effect of 1 to 10 mg/kg s.c. morphine on threshold repeatedly during 2 to 4 weeks and found no tolerance for this effect of morphine. Although they administered 8 to 10 mg/kg daily after the test sessions, the lower dose given the next day before the test remained effective on threshold. Van Wolfswinkel and Van

Ree (1985b) compared the effect of graded doses of morphine (0.3–5 mg/kg s.c.) using three different procedures to measure the threshold of ICSS in rats with electrodes in the VTA. The procedures were 1) determination of response rate, i.e., the number of responses, to high and threshold currents; 2) measuring threshold current when the response rate was kept low and relatively constant; and 3) determination of "behavioral" threshold using a two-lever procedure in which a response on one lever resulted in a reset of the decreasing current to a high-current contingent on a response to the other lever (see also, Stein and Ray, 1960). Different groups of animals were used for the three procedures and five doses of morphine were administered in increasing dose, spaced at least for 2 days. As compared to placebo treatment the previous day, morphine induced a slight decrease (low doses) and increase (high dose) of the threshold current in the response rate procedure, no effect in the constant response rate procedure, and a dose-related decrease of the threshold current in the behavioral threshold procedure. During this latter procedure, no change in response rate was observed after morphine treatment. A similar effect of morphine in the behavioral threshold procedure was observed in rats used before for the two other procedures. The behavioral threshold procedure, in which the rat can select its own threshold current, is theoretically the most insensitive to nonreward-related motor performance effects. Response rate is not used for calculation of the threshold and was not affected by morphine treatment (see also, Zarevics and Setler, 1979). In subsequent experiments, using the same behavioral threshold procedure, no tolerance to the morphine-induced decrease in threshold was observed when morphine (5 mg/kg s.c.) was administered for 15 days before ICSS testing (Van Wolfswinkel et al., 1985). In this experiment, a decrease in response rate was found, but only during the first 2 days of morphine treatment. Thus, enhanced brain reinforcement can be observed after acute and chronic treatment with morphine when a response rate-insensitive procedure is used to measure ICSS behavior. This conclusion corroborates with other experiments using threshold determinations of ICSS (Esposito and Kornetsky, 1977, 1978; Esposito et al., 1979; Nazzaro et al., 1981; Kornetsky and Bain, 1983).

When the response rate is measured as a dependent variable for determining ICSS, the effect of morphine depends on the drug dose, the time between treatment and testing, and whether or not the animals are drug-naive. In general, systemically administered low doses of morphine (<3 mg/kg) can increase, whereas larger doses disrupt responding in the period shortly after administration (Adams et al., 1972; Glick and Rapaport, 1974; Wauquier and Niemegeers, 1976; Schaefer and Holtzman, 1977; Weibel and Wolf, 1979; Van Wolfswinkel and Van Ree, 1985b). This disruption is followed by an increase in ICSS responding 2 to 6 h after morphine treatment (Adams et al., 1972; Lorens and Mitch-

ell, 1973; Lorens, 1976). This delayed facilitation is enhanced and present earlier after repeated injection of morphine (Adams et al., 1972; Kelley and Reid, 1977; Schaefer and Holtzman, 1977). Using a procedure in which the stimulus frequency of the electrical current is varied yielding a response rate-frequency function that resembles the traditional pharmacological dose-response curve, morphine induced a leftward shift of the response rate-frequency function, indicating facilitation of ICSS (Rompré and Wise, 1989; Bauco et al., 1993; Carlezon and Wise, 1993a; Wise, 1996). In tolerant animals, an enhancement of ICSS has consistently been found (Lorens and Mitchell, 1973; Bush et al., 1976; Weibel and Wolf, 1979; Van Wolfswinkel et al., 1985).

The facilitation of ICSS by morphine is mimicked by other opioids administered systemically, as shown by experiments in which heroin, 6-acetylmorphine, methadone, levorphanol, or pentazocine was tested (Kornetsky et al., 1979; Weibel and Wolf, 1979; Bozarth et al., 1980; Stutz et al., 1980; Gerber et al., 1981; Preshaw et al., 1982; Schenk and Nawiesniak, 1985; Hubner and Kornetsky, 1992). The facilitation of ICSS appeared to be stereoselective in that dextrorphan did not enhance ICSS, and opioid antagonists blocked the effect (Weibel and Wolf, 1979). Thus, opioid receptors are probably involved in the opioid-induced facilitation of ICSS.

From the data, it can be concluded that morphine and other opioids can facilitate ICSS reward and that no tolerance developed for the facilitating effect of morphine. Depending on the procedure used, an initial depression of behavior is present in morphine-naive animals, but tolerance to this probably nonreward-related effect develops upon repeated drug administration.

In experiments in which systemically administered morphine facilitated ICSS, the electrodes were in general implanted in the MFB/LH area or in the VTA. Although a direct comparison between these areas with respect to morphine action has not been performed, the obtained data are quite comparable: doses of morphine around 1 mg/kg and higher facilitated ICSS. In some studies other brain sites have been studied. When the electrodes were implanted in the medial prefrontal cortex, locus ceruleus, dorsal raphe nucleus, or mesencephalic central gray, similar effects of morphine were found (Lorens, 1976; Liebman and Segal, 1977; Esposito et al., 1979; Jackler et al., 1979; Nelson et al., 1981; Schenk et al., 1981). But a facilitation of ICSS by morphine was not present when the electrodes were implanted in the substantia nigra or in the medial part of the anterior prefrontal cortex (Nazzaro et al., 1981; Corbett, 1992). Thus, not all sites from which ICSS behavior can be elicited seem to be influenced by systemically administered morphine.

The facilitating effect of systemically administered opioids was mimicked when relatively low doses of morphine or levorphanol, but not dextrorphan, were injected directly into the brain ventricle, implicating central opi-

oid receptors in this opioid action (Weibel and Wolf, 1979; Shaw et al., 1984). A number of studies have addressed the site of action of morphine and other opioids in facilitating ICSS behavior. Morphine (1 μg) injected bilaterally into the ventral tegmental/substantia nigra area but not in the NAC or the striatum facilitated ICSS behavior elicited from electrodes placed in the MFB (Broekkamp and Van Rossum, 1975; Broekkamp et al., 1976; Broekkamp and Phillips, 1979). Morphine was effective at a dose of 200 ng, but not of 50 ng, and the drug effect was blocked by systemically administered naloxone. The effect of morphine was mimicked by injection of [D-Ala^2]-Met-enkephalinamide into the same area. A dose-dependent decrease in the frequency threshold for ICSS from the MFB was found after injecting morphine into the VTA (Rompré and Wise, 1989; Bauco et al., 1993). Neither sensitization nor tolerance was observed following repeated morphine injection (Bauco et al., 1993).

Selective μ-, δ-, and κ-opioid receptor ligands have been injected into the VTA in rats with electrodes in the MFB. The effects on ICSS were, however, not consistent and both facilitating effects and no effects have been reported (Jenck et al., 1987; Heidbreder et al., 1992; Singh et al., 1994). Other studies have shown stimulating effects of the μ-opioid receptor ligand DAMGO injected into the lateral accumbens core or the caudal ventral pallidum and of the δ-specific ligand DPDPE injected into the caudal ventral pallidum or ventromedial striatum (Johnson et al., 1993, 1995a; Johnson and Stellar, 1994). ICSS behavior elicited from electrodes in the NAC was facilitated by morphine injected in a dose of 50 ng or higher into the VTA using the behavioral threshold method (Van Wolfswinkel and Van Ree, 1985a). Interestingly, morphine injected into the NAC did not affect ICSS elicited from the VTA (Van Wolfswinkel and Van Ree, 1985a). Injection of specific μ-, δ-, or κ-opioid receptor ligands, DAMGO, [D-Ala^2,D-Met^5]-enkephalin, and dynorphin B, respectively, into the VTA facilitated ICSS from this area, whereas the same ligands were ineffective when injected into the MFB (Singh et al., 1994). A decrease of threshold for ICSS from the VTA was found when the μ-opioid receptor agonist DAMGO or the δ-opioid receptor agonist DPDPE was injected into the NAC. This effect was blocked by peripheral administration of the δ-antagonist naltrindole (Duvauchelle et al., 1996; Duvauchelle et al., 1997). Finally, morphine injected into the medial prefrontal cortex did not modify ICSS from this area (Shaw et al., 1984). Taken together, the data collected so far provide evidence that the VTA is a sensitive site for morphine and other opioids in facilitating ICSS reinforcement, although this may not be the only brain site.

With respect to the neurochemical systems involved in opioid-induced facilitation of ICSS, little information is available with the exception of the endogenous opioids and DA systems (see *VII. Brain DA and Opioid Drugs of*

Abuse). Blockade of NMDA receptors by MK-801 potentiated the morphine-induced facilitation of ICSS (Carlezon and Wise, 1993a).

B. Endogenous Opioids

A useful approach to investigate the role of endogenous opioids in certain behaviors is to analyze the effects of opioid antagonists on that behavior. A number of studies have been performed dealing with opioid antagonists and ICSS. The first reports were on the opioid antagonist naloxone and ICSS for electrodes implanted in the MFB/LH area (Wauquir et al., 1974; Holtzman, 1976; Goldstein and Malick, 1977; Van der Kooy et al., 1977). In general, no marked effects of naloxone were found. In contrast, a large decrease of ICSS behavior by naloxone was reported when the electrodes were implanted in the central gray area of the midbrain (Belluzzi and Stein, 1977). After these initial reports, several studies have addressed the reason for these equivocal results. The data obtained have extensively been discussed in a review by Schaefer (1988).

It appears that the effect of opioid antagonists depends on the site of the stimulation electrode. In addition to the central gray area, decreases after naloxone have been reported when the electrodes were implanted in the locus ceruleus, substantia nigra, septal area, paratenial nucleus of the thalamus, dentate gyrus, NAC, medial entorhinal cortex, or amygdala (for references, see Schaefer, 1988; Trujillo et al., 1989a). The effects were, however, not always consistently found among the different laboratories and the effective dose of naloxone varied between less than 1 mg/kg to 10 mg/kg. It seems that the MFB/LH area is the least reliable site for the effects of opioid antagonists. Other factors influencing the effect of naloxone on ICSS are the amount of effort required of the animal but not the response difficulty (Trujillo et al., 1989c) and the schedule of reinforcement. The studies cited above used the continuous reinforcement schedule. When FR schedules were used, opioid antagonists produced marked dose-dependent decreases in the rate of lever-pressing (Schaefer and Michael, 1981, 1985; West et al., 1983). Also using this procedure, it appeared that the central gray area was a much more sensitive site for opioid antagonists than the MFB/LH area. Furthermore, the effectiveness of naloxone increased when the FR requirement was raised. The effect of naloxone persisted for about 2 h, which is consistent with the duration of action of this drug. Thus, intermittent reinforcement schedules can reliably disclose the effects of naloxone (Franklin and Robertson, 1982).

Another interesting observation is that the effect of opioid antagonists seem to be stronger in longer than in shorter test sessions of ICSS. This could indicate that the antagonists block the reinforcing value of ICSS, resulting in an extinction-like pattern of responding (Katz, 1981; Trujillo et al., 1989b). Only a few studies have been performed using rate-independent procedures of ICSS. Comparing these procedures, measuring the threshold for ICSS in rats with electrodes in the VTA, it was consistently found that a rather high dose of naloxone (10 mg/kg s.c.) raised the threshold for ICSS (Van Wolfswinkel and Van Ree, 1985b). Using the behavioral threshold procedure and testing and treating the animals repeatedly with naloxone, it appeared that the naloxone-induced increase of threshold became more pronounced during the 3 weeks of the experiment (Van Wolfswinkel et al., 1985). Interestingly, this effect persisted for at least 3 days after discontinuation of naloxone treatment. It was concluded that blockade of opioid receptors may induce long-term changes in the setpoint of ICSS. Accordingly, continuous s.c. administration of naloxone shifted ventral tegmental ICSS rate-frequency curves to the right, without suppressing behavioral performance (Hawkins and Stein, 1991). Since the acute effect of naloxone on the threshold was lower in animals more experienced with ICSS behavior, a study was performed on acquisition of the behavioral threshold procedure (Van Wolfswinkel and Van Ree, 1985c). It was found that this acquisition was disrupted by repeated treatment with naloxone, whereas the acquisition of a comparable food reinforced behavior was not affected by naloxone treatment. It has been argued that these data are consistent with those obtained with the FR schedule of reinforcement (Schaefer, 1988).

Most studies have used the antagonist naloxone. But similar effects have been reported with naltrexone and diprenorphine (Schaefer and Michael, 1981, 1985, 1988a). With respect to diprenorphine, opposite effects, i.e., an increase of responding for ICSS, have been found as well (Pollerberg et al., 1983; LaGasse et al., 1987). The effects of opioid antagonists are likely to be produced in the CNS, since both naloxone methobromide and naltrexone methobromide, compounds that rarely cross the blood-brain barrier, were without effect after systemic administration (Schaefer and Michael, 1985; Trujillo et al., 1989a). Some studies have been performed with mixed opioid agonist-antagonists. Decreased responding for ICSS has been reported for cyclazocine, nalorphine, and pentazocine (Holtzman, 1976; Schaefer, 1988). However, in another study, a lowering of the threshold for ICSS after nalbuphine or pentazocine was observed and no changes in threshold after cyclazocine or nalorphine (Kornetsky et al., 1979). Intracerebroventricular administration of high doses of the δ-opioid antagonist naltrindole, but not the μ-antagonist D-Tic-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH$_2$ and the κ-antagonist nor-BNI raised the ICSS threshold (Carr and Papadouka, 1994; Carr, 1996).

Chronic food restriction facilitated ICSS from the LH, as has been shown for drug self-administration (Carr and Wolinsky, 1993; Carr, 1996). This facilitatory effect was blocked by i.c.v. naltrexone, the μ antagonist TCTAP, and the κ antagonist nor-BNI, suggesting that

μ-, and κ-opioid receptors are involved in this facilitation (Carr and Papadouka, 1994; Carr, 1996).

Strains of rats, selectively bred for high versus low rate of lateral hypothalamic ICSS were analyzed for their density of μ-opioid receptors in discrete brain areas using the ligand [³H]DAMGO and in vitro autoradiography. The high-rate animals showed a higher and lower density of μ-opioid receptors in the ventral hippocampus and NAC, respectively, as compared to the low-rate animals (Gross-Isseroff et al., 1992). In addition, there is some evidence that endogenous opioids are released during self-stimulation of the VTA, as measured by the in vivo receptor occupancy procedure (Stein, 1993).

In conclusion, there seems to be evidence that endogenous opioid systems are involved in ICSS. The data collected so far point to a modulatory role rather than that reward from ICSS is mediated by endogenous opioids. More studies are needed, in particular after chronic blockade of endogenous opioids, to delineate more precisely the significance of endogenous opioids for ICSS.

V. Conditioned Place Preference

A. Opioid Place Preference

Beach (1957) was the first to report that morphine elicits conditioned place preference. In that study it was shown that in rats made physically dependent upon morphine, administration of morphine during extensive training (12–22 days of conditioning sessions, using training doses of 5–20 mg/kg morphine, injected either s.c. or i.p.) resulted in preferences for the previously nonpreferred side of a test box. During preference testing, morphine was still administered to the animals. Interestingly, a place preference was observed both when, according to the conditioning schedule, the animals were expecting an injection with morphine in the conditioned compartment ("needing morphine") or when they had been injected with morphine 10 min to 4 h before the test session ("sated for morphine"). These results suggested that both relief from morphine withdrawal and morphine's positive affective properties could contribute to the establishment of conditioned place preference. The place preference induced by morphine withdrawal relief appeared to persist for 3 weeks. These findings were replicated in a later study investigating the involvement of monoamines in withdrawal relief-induced conditioned place preference (Schwartz and Marchok, 1974). In the late 1970s, morphine-induced conditioned place preference was first reported in animals not previously made physically dependent on morphine (Rossi and Reid, 1976; Katz and Gormezano, 1979). It was observed that when rats were conditioned at times when morphine (10 mg/kg s.c.) was expected to facilitate ICSS (1–4.5 h, but not 7 h postinjection), conditioned place preference was induced (Rossi and Reid, 1976). Another study showed that as few as three conditioning sessions with morphine or an enkephalin an-

alog, administered i.c.v., were sufficient to produce place preference (Katz and Gormezano, 1979).

Using morphine and naloxone as conditioning drugs, Mucha and colleagues (Mucha et al., 1982; Mucha and Iversen, 1984; Mucha and Herz, 1986) have systematically investigated several methodological variables that can influence opioid-induced place-conditioning, e.g., dose of drug, route of administration, trial duration, number of conditioning trials, and stereospecificity of the opioids. Using four conditioning trials and i.v. administration of morphine, significant place preference was found with doses ranging from 0.08 to 10 mg/kg. Trial duration of 10 to 90 min induced similar levels of place preference. It appeared that one conditioning trial with 4 mg/kg morphine was sufficient to induce place preference. When morphine was administered s.c., place preference was found with 0.2 to 5 mg/kg, whereas 0.04 mg/kg was ineffective. Naloxone induced place aversion, in doses ranging from 0.02 to 2 mg/kg, and 0.1 to 45 mg/kg, when administered s.c. or i.p., respectively. Upon s.c. administration, three trials with morphine (1 mg/kg) or naloxone (0.5 mg/kg) were necessary to induce a significant place preference or aversion, respectively (Mucha et al., 1982; Mucha and Iversen, 1984). The development of place preference induced by morphine (0.5–2 mg/kg i.v.) was inhibited by naloxone (2 mg/kg i.p.) (Mucha et al., 1982). Stereospecificity of opioid-induced place-conditioning was demonstrated using levorphanol, which, in contrast to its inactive stereoisomer dextrorphan, induced place preference (Mucha et al., 1982; Mucha and Herz, 1986). In addition, although conditioning with (−)-morphine and (−)-naloxone caused place preference and aversion, respectively, (+)-morphine and (+)-naloxone were ineffective (Mucha et al., 1982).

In a follow-up study, the influence of environmental novelty and interoceptive states on morphine-induced place preference was investigated (Mucha and Iversen, 1984). It appeared that animals conditioned with morphine (4 trials, 1 mg/kg s.c.) and tested after injection of saline or morphine (1 mg/kg s.c.) displayed nearly identical levels of place preference. This seems to rule out any effects of state-dependent learning on the expression of morphine-induced place preference. Morphine-induced place-conditioning was also performed in a three-compartment apparatus, with one compartment being completely novel to the animals on the test day. Here, a clear preference for the morphine-paired side, over both the novel and the familiar saline-paired part of the apparatus, was observed. In this experiment, the animals spent more time (albeit not statistically significant) in the novel compartment, as compared to the saline-paired environment. In a subsequent experiment, rats were placed four times in one side of the two-compartment apparatus without any injections, and no preference for the novel or familiar side was found. However, when conditioning was performed with morphine,

without intervening saline trials, a clear preference of the morphine-paired over the novel environment was found on the test day. These findings seem to exclude any major influence of exploration or environmental novelty on morphine-induced conditioned place preference. In this study, it was also shown that testing at two postconditioning intervals (1 day or 1 month) did not affect the strength of morphine-induced place-conditioning (Mucha and Iversen, 1984).

The studies described above clearly demonstrate that morphine reliably induces conditioned place preference and naloxone place aversion (Mucha et al., 1982; Mucha and Iversen, 1984; Mucha and Herz, 1986). These effects are most likely mediated through opioid receptors, with only marginal interference of state-dependent learning and environmental novelty or familiarity.

1. Opioid Receptor Types. Regarding the involvement of opioid receptor types, there is a vast amount of evidence that stimulation of μ receptors induces conditioned place preference. After systemic injections of etonitazene, etorphine, fentanyl, heroin, levorphanol, methadone, morphine, morphine-6-glucuronide, and sufentanil, all of which can be regarded to be more or less specific agonists for μ-opioid receptors, conditioned place preference has been reported (Bozarth and Wise, 1981a; Mucha et al., 1982; Spyraki et al., 1983; Mucha and Iversen, 1984; Iwamoto, 1985; Mucha and Herz, 1985; Amalric et al., 1987; Bozarth, 1987a; Shippenberg et al., 1987, 1993; Corrigall and Linseman, 1988; Hand et al., 1989; Kelsey et al., 1989; Abbott and Franklin, 1991; Shippenberg and Herz, 1991; Sala et al., 1992; Funada et al., 1993; Steinpreis et al., 1996). Place preference could be induced by i.c.v. injections of the specific μ agonist DAMGO, which was blocked with the μ antagonist D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Phe-Thr-NH$_2$ (CTOP), but not the δ antagonist ICI 174,864 (Bals-Kubik et al., 1990; Suzuki et al., 1991). In addition, place preference induced by injections of morphine or heroin could be blocked with the relatively nonspecific opioid antagonists naloxone or naltrexone, the μ_1 antagonist naloxonazine, but not with the δ antagonists ICI 174,864 or naltrindole, or the κ antagonist nor-BNI (Mucha et al., 1982; Bardo and Neisewander, 1986, 1987; Shippenberg et al., 1987; Hand et al., 1989; Funada et al., 1993; Piepponen et al., 1997, but see Suzuki et al., 1994b; Kamei et al., 1997). Uncoupling of μ receptors from their G proteins using i.c.v. administered pertussis toxin appeared to inhibit the development of place preference induced by i.c.v. morphine or DAMGO (Suzuki et al., 1991). Recently, it has been shown that in knockout mice lacking the μ-opioid receptor gene, morphine did not induce conditioned place preference (Matthes et al., 1996). In addition to full μ-opioid agonists, conditioned place preference has also been observed with the mixed μ-opioid agonist-antagonist buprenorphine (Gaiardi et al., 1997).

Blockade of μ receptors induces place aversion. Systemic injections of naloxone or naltrexone and i.c.v. injections of CTOP, naloxone, or methylnaloxonium (an analog of naloxone that does not cross the blood-brain barrier) induced place aversion (Phillips and LePiane, 1980; Bozarth and Wise, 1981a; Mucha and Iversen, 1984; Iwamoto, 1985; Mucha and Herz, 1985; Mucha et al., 1985; Amalric et al., 1987; Bechara et al., 1987; Mucha and Walker, 1987; Hand et al., 1988; Shippenberg and Herz, 1988, 1991; Bals-Kubik et al., 1989; Abbott and Franklin, 1991; Gerrits et al., 1995). Peripheral injection of methylnaloxonium had no effect on place-conditioning, suggesting a central site of action for the aversive effects of opioid antagonists (Heinrichs and Martinez, 1986; Hand et al., 1988). When naloxone was administered before testing, it appeared to enhance morphine-induced place preference (Neisewander et al., 1990). Bremazocine, which combines μ antagonist with agonist effects at both κ receptors and the μ-δ receptor complex (Heijna et al., 1989; Schoffelmeer et al., 1992), also induced place aversion (Iwamoto, 1985; Mucha and Herz, 1985). The δ antagonists ICI 174,864, naltrindole, 7-benzylidenenaltrexone (BNTX: δ_1 antagonist), and naltriben (δ_2 antagonist) and the κ antagonist nor-BNI did not induce place-conditioning (Shippenberg et al., 1987; Bals-Kubik et al., 1989, 1990; Suzuki et al., 1994b; De Vries et al., 1995).

The capacity of naloxone to induce conditioned place aversion was reduced in rats with lesions of the arcuate nucleus of the hypothalamus. This suggests that the aversive effects of naloxone involved antagonism of the action of central β-endorphin, especially since decreasing peripheral β-endorphin levels by treatment with dexamethasone had no such effect. Arcuate nucleus lesions did not affect the place-conditioning effects of morphine or the κ-opioid agonist U50,488H (Mucha et al., 1985).

Regarding the effects of endogenous opioid peptides on place-conditioning, administration of enkephalinase inhibitors was ineffective (Noble et al., 1993; Ågmo et al., 1994). Systemically, as well as i.c.v. injected β-endorphin induced place preference, which was abolished with the μ antagonist CTOP, but also by the δ antagonist ICI 174,864, suggesting that also δ receptors are involved in β-endorphin-induced place preference (Amalric et al., 1987; Bals-Kubik et al., 1990; Spanagel et al., 1991). The novel opioid-like neuropeptide orphanin FQ was found to induce neither conditioned place preference nor aversion (Devine et al., 1996).

Involvement of δ receptors in opioid place-conditioning was further demonstrated in studies showing that i.c.v. DPDPE induced place preference, which could be abolished by ICI 174,864 but not CTOP (Shippenberg et al., 1987; Bals-Kubik et al., 1990; Suzuki et al., 1991). The nonpeptide δ antagonists BW373U86 [($\pm$)-4-((α-R*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide] and SNC-80

[(+)-4-[(α-R^*)-α-((2S^*,5R^*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide] could induce conditioned place preference, which could be prevented by pretreatment with naltrindole (Longoni et al., 1998). In addition, morphine-induced place preference, which could not be blocked with the δ antagonist ICI 174,864 (Shippenberg et al., 1987) was shown to be abolished by the nonspecific δ antagonist naltrindole as well as by the δ receptor subtype antagonists BNTX (δ_1) and naltriben (δ_2) (Suzuki et al., 1994b; Kamei et al., 1997, but see Piepponen et al., 1997). In addition, the capacity of morphine to elicit conditioned place preference was found to be profoundly reduced in mice pretreated i.c.v. with antisense oligodeoxynucleotide to δ receptor mRNA (Suzuki et al., 1997a). Recently, it was also shown that both δ_1 and δ_2 receptor subtypes are involved in opioid place-conditioning, since both the δ_1 agonist DPDPE and the δ_2 agonist [D-Ala^2]-deltorphin II induced place preference, both of which could be inhibited by specific antagonists (BNTX and naltriben, respectively) (Suzuki et al., 1996c, 1997c). Treatment with the nonpeptide δ agonist TAN-67 did not induce place preference but enhanced the ability of morphine to induce conditioned place preference. This effect of TAN-67 could be antagonized with naltrindole, a nonselective δ antagonist as well as BNTX and naltriben, implicating both δ receptor subtypes (δ_1 and δ_2) in this effect (Suzuki et al., 1996b; Kamei et al., 1997). Similar to μ receptors, uncoupling of δ receptors from G proteins with pertussis toxin, administered i.c.v., inhibited the development of DPDPE-induced place preference (Suzuki et al., 1991).

Stimulation of κ-opioid receptors induces place aversion. Systemic and i.c.v. injections of the κ-opioid agonists U50,488H, U69,593, and E-2078 and the opioid agonist-antagonist bremazocine induced aversion (Iwamoto, 1985; Mucha and Herz, 1985; Mucha et al., 1985; Shippenberg and Herz, 1987, 1988, 1991; Bals-Kubik et al., 1989; Funada et al., 1993; Shippenberg et al., 1993). In addition, morphine-induced preference is abolished by the κ agonists U50,488H and E-2078 (Funada et al., 1993; Bolanos et al., 1996). Intracerebroventricular dynorphin A(1–17) has been shown to induce naloxone-antagonizable place preference (Iwamoto, 1988). This effect is, however, not necessarily mediated through κ receptors, since dynorphin A(1–17) has affinity for μ receptors as well. In addition, metabolization of this peptide could yield a product with agonist activity at δ receptors (Höllt, 1986).

There seems to be general agreement that stimulation of μ-opioid receptors induces conditioned place preference, whereas blockade of μ receptors induces place aversion. Stimulation of κ receptors induces conditioned place aversion, but blockade of κ receptors does not seem to induce significant place-conditioning. With regard to the involvement of δ receptors, stimulation of δ receptors with specific ligands induces place preference, whereas blockade of δ receptor has no major effects on place-conditioning. However, the role of δ receptors in the place preference induced by morphine is not clear.

2. Sites of Action. Studies into possible sites of action for opioids to induce place-conditioning have found two main areas: the NAC and VTA. With respect to the latter, injections of morphine, an enkephalin analog, and DAMGO into the VTA have been shown to cause place preference (Phillips and LePiane, 1980, 1982; Phillips et al., 1983; Bozarth, 1987b; Bals-Kubik et al., 1993; Olmstead and Franklin, 1997b). Injections of morphine in sites adjacent to the VTA were without effect (Phillips and LePiane, 1980; Bozarth, 1987b; Olmstead and Franklin, 1997b). The place preferences induced by intra-VTA-administered morphine or [D-Ala^2]-metenkephalin could be abolished by systemic pretreatment with naloxone (Phillips and LePiane, 1980, 1982) while preference induced by systemic morphine could be blocked by intra-VTA injections of naloxone methiodide (Olmstead and Franklin, 1997b). Intra-VTA injections of the μ-opioid antagonist CTOP or naloxone induced place aversion, which were inhibited by 6-hydroxydopamine (6-OHDA)-induced lesions of the NAC (Shippenberg and Bals-Kubik, 1995). The main effect of μ receptor stimulation in the VTA seems to be inhibition of γ-aminobutyric acid release (Johnson and North, 1992; Klitenick et al., 1992). In this respect, it is worth noting that the place preference induced by peripheral administration of morphine could be prevented with intra-VTA infusion of the γ-aminobutyric acid type B agonist baclofen (Tsuji et al., 1996). Infusion of κ agonists (U50,488H, E-2078) into the VTA induced place aversion as well (Bals-Kubik et al., 1993).

Morphine administered into the NAC was shown to result in place preference (Van der Kooy et al., 1982), but negative results with morphine or DAMGO administered into the NAC have also been published (Bals-Kubik et al., 1993; Olmstead and Franklin, 1997b; Schildein et al., 1998). Electrolytic as well as extensive NMDA- or kainic acid-induced lesions of the NAC have been shown to inhibit the development of morphine-induced place preference (Kelsey et al., 1989; Olmstead and Franklin, 1996). Similar to the VTA, administration of the μ antagonist CTOP or naloxone as well as the κ agonists U50,488H and E-2078 into the NAC resulted in place aversions (Bals-Kubik et al., 1993; Shippenberg and Bals-Kubik, 1995). 6-OHDA-induced lesions of the NAC abolished the place preference induced by peripheral injections of morphine and the place aversions induced by U69,593 (Shippenberg et al., 1993, but see Olmstead and Franklin, 1997a) but not the aversions induced by intra-NAC-injected CTOP or naloxone (Shippenberg and Bals-Kubik, 1995).

There are a number of other sites that have been proposed to mediate the place preference induced by morphine or enkephalin and place aversion induced by κ-opioid agonists, respectively, but the involvement of these sites has not been thoroughly investigated. For

morphine- or enkephalin-induced place preference, these sites include the lateral hypothalamus, periaqueductal gray, hippocampus, medial preoptic area, and pedunculopontine nucleus (Van der Kooy et al., 1982; Corrigall and Linseman, 1988; Bechara and Van der Kooy, 1989; Ågmo and Gomez, 1991; Olmstead and Franklin, 1993). It should be noted, however, that with respect to the lateral hypothalamus, periaqueductal gray, and hippocampus, high doses of opioids were necessary to induce place preference. In addition, a recent microinjection study suggested that of these sites, only injection of morphine into the periaqueductal gray was effective in inducing conditioned place preference (Olmstead and Franklin, 1997b). The pedunculopontine nucleus represents an additional site through which morphine might act to induce conditioned place preference. The induction of conditioned place preference induced by morphine could be prevented by lesions of the pedunculopontine nucleus (Bechara and Van der Kooy, 1989; Olmstead and Franklin, 1993, 1997a). However, microinjection of morphine into this area failed to induce place preference, suggesting that the pedunculopontine nucleus is located downstream from the site where morphine interacts with opioid receptors to induce place preference (Olmstead and Franklin, 1997b). Place preference has also been reported following injection of morphine into the substantia nigra, whereas morphine-6-glucuronide, DAMGO, DPDPE, and U50,488H were ineffective in this respect (Bals-Kubik et al., 1993; Baumeister et al., 1993). Injection of morphine or DAMGO into the caudate putamen, amygdala, medial prefrontal cortex, ventral pallidum, and nucleus ambiguus has been shown to be ineffective in inducing place preference (Van der Kooy et al., 1982; Bals-Kubik et al., 1993; Olmstead and Franklin, 1997b). In addition, lesions of the caudate putamen, lateral amygdala, or ventral pallidum were ineffective in preventing the development of morphine-induced place preference, whereas lesions of the fornix or periaqueductal gray rendered morphine place preference state-dependent (Olmstead and Franklin, 1997a). Additional central sites into which κ agonists (U50,488H, E-2078) induced aversion were the lateral hypothalamus and medial prefrontal cortex (Bals-Kubik et al., 1993). Naloxone injected into the caudate putamen or medial prefrontal cortex was ineffective in producing place aversion (Shippenberg and Bals-Kubik, 1995).

Taken together, a major role can be attributed to both VTA and NAC in the preference and aversion induced by μ-opioid agonists and antagonists, respectively. The case seems to be stronger for the VTA, in view of the failure of some studies to observe a place preference upon intra-NAC μ-opioid administration and of the finding that higher doses of morphine are necessary to elicit place preference in the NAC as compared to the VTA. As for μ opioids, the place aversion induced by κ agonists seems to utilize both VTA and NAC.

3. Brain Neurochemical Systems. In this section, the involvement of various neuronal systems in opioid place preference is discussed, with the exception of DA (see *VII. Brain DA and Opioid Drugs of Abuse).*

Involvement of noradrenergic systems in opioid place preference was mainly shown in the case of withdrawal-induced place aversion, which could be blocked with the β adrenoceptor antagonists propranolol and atenolol (Harris and Aston-Jones, 1993) as well as with the α_2 adrenoceptor agonist clonidine (Kosten, 1994; Nader and Van der Kooy, 1996; Schulteis et al., 1998). However, clonidine was found to be ineffective in influencing the expression of withdrawal-induced place aversion (Schulteis et al., 1998). Clonidine was also found to inhibit the acquisition of heroin-induced conditioned place preference, but peripheral and central noradrenaline depletion were reported not to affect heroin-induced place preference (Spyraki et al., 1983; Hand et al., 1989).

Brain 5-HT systems have been suggested to be involved in opioid-place preference. Thus, both antagonists of $5\text{-}HT_2$ (ritanserin) and $5\text{-}HT_3$ receptors (ondansetron, MDL 72222), but not $5\text{-}HT_4$ receptors were found to inhibit morphine-induced place preference (Nomikos and Spyraki, 1988; Carboni et al., 1989; Higgins et al., 1992a; Bisaga et al., 1993). The NAC has been suggested to be a possible site for this effect, since lesioning 5-HT terminals was shown to inhibit morphine-induced place preference (Spyraki et al., 1988). The 5-HT reuptake inhibitor zimelidine was found not to affect morphine-induced conditioned place preference (Kruszewska et al., 1986).

Conflicting results have been reported for the effects of benzodiazepines on opioid place-conditioning. Although the benzodiazepine triazolam and the benzodiazepine antagonist Ro 15-1788 have been reported not to affect morphine-induced place preference, it was also found that diazepam inhibited and the benzodiazepine inverse agonist methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate enhanced the development of morphine place preference (Pettit et al., 1989; Bilsky et al., 1990; Suzuki et al., 1995c; Will et al., 1998).

Glutamate antagonists, and especially NMDA antagonists, have been reported to inhibit the development of morphine-induced place preference (Bespalov et al., 1994; Tzschentke and Schmidt, 1995, 1997; Del Pozo et al., 1996; Kim et al., 1996; Popik and Danysz, 1997). In addition, the presynaptic glutamate release inhibitor riluzole also prevented the development of morphine place preference (Tzschentke and Schmidt, 1998). Infusion of the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) antagonist 6,7-dinitroquinoxaline-2,3-dione into the NAC did not influence morphine's capacity to induce conditioned place preference (Layer et al., 1993). Interestingly, intra-VTA infusion of a viral vector expressing GluR1, an AMPA receptor subunit previously shown to be up-regulated by morphine administration, was shown to increase the sensitivity to

the effects of morphine to induce conditioned place preference (Carlezon et al., 1997). The proposed functional NMDA antagonist acamprosate was found to prevent the acquisition of naloxone-precipitated morphine withdrawal-induced place aversion (Kratzer and Schmidt, 1998).

Administration of an antagonist of the CB1 cannabinoid receptor, SR 141716 (*N*-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide) blocked the development of morphine place preference (Chaperon et al., 1998). In addition, prenatal exposure to Δ^9-tetrahydrocannabinol appeared to cause increased sensitivity to the ability of morphine to induce conditioned place preference (Rubio et al., 1998).

Opposite roles for different types of cholecystokinin (CCK) receptors in the induction of morphine-induced place preference have been suggested. Antagonists of CCK-A receptors, as well as mixed CCK receptor antagonists, appeared to block the development of morphine-induced conditioned place preference (Higgins et al., 1992b; Singh et al., 1996a,b). In contrast, blockade of CCK-B receptors was reported to actually enhance opioid-induced place preference, although in another study a CCK-B antagonist appeared to have no such effect (Higgins et al., 1992b; Singh et al., 1996b; Valverde et al., 1996). When administered during the development of morphine physical dependence, CCK-B antagonists, but not CCK-A antagonists appeared to inhibit the place aversion induced by subsequent treatment with naloxone (Valverde and Roques, 1998).

An inhibitory influence of histamine receptor stimulation on morphine-induced place-conditioning was suggested in a study which showed that administration of a histamine H2 antagonist, which by itself also induced place preference, potentiated the effects of morphine on place-conditioning. In addition, a histamine synthesis inhibitor was also shown to potentiate, whereas administration of a histamine precursor inhibited morphine-induced place preference (Suzuki et al., 1995b).

The induction of place aversion induced by lithium chloride was found to be blocked by coadministration of naloxone as well as previous lesions of the mediobasal hypothalamus, which markedly reduced brain β-endorphin levels (Shippenberg et al., 1988b). Chronic administration of a lithium-containing diet, which did not modify central β-endorphin levels or release, was shown to inhibit place preference and aversion induced by morphine or naloxone, respectively. The effects of amphetamine and U69,593 on place-conditioning were not modified by lithium, suggesting that lithium might counteract the effects of μ receptor ligands (Shippenberg and Herz, 1991).

Calcium channel blockers have been shown to inhibit acquisition of morphine-place preference (Kuzmin et al., 1992a; Biala and Langwinski, 1996), as was also shown for nitric oxide synthase inhibitors (Kivastik et al., 1996). Calcium-dependent endopeptidase inhibitors were found to have a similar effect (Lyupina et al., 1996).

Inhibition of morphine-induced place preference was also found with cyclosporine A; this effect was absent in a μ-opioid receptor-deficient mouse strain (Suzuki et al., 1993). In addition, inflammation blocked the development of morphine place preference, whereas adrenalectomy was found to potentiate it (Suzuki et al., 1995a, 1996a). In diabetic mice, the capacity of morphine to induce place preference was enhanced, possibly through increased δ-opioid receptor function (Kamei et al., 1997). Naloxone blocked the place preference induced by Substance P or a Substance P analog (Hasenohrl et al., 1991).

The involvement of nondopaminergic neurotransmitter and neuromodulator systems in opioid place-conditioning has only been sparsely investigated. Of these systems, a role for 5-HT and CCK systems in opioid place-conditioning can be proposed, as well as for NMDA receptors. With respect to the latter system, the effects of NMDA antagonists on morphine-induced place-conditioning are not due to the induction of state-dependent learning (Tzschentke and Schmidt, 1997), and it has been shown that in self-administration and ICSS models, NMDA receptor antagonists potentiate the reinforcing properties of morphine and cocaine (Carlezon and Wise, 1993a; Ranaldi et al., 1996, 1997). Thus, it is likely that the effects of NMDA antagonists on morphine-induced place-conditioning reflect the disruptive effects of NMDA antagonists on learning (Morris et al., 1986; Bliss and Collingridge, 1993).

B. Variables Interfering with Opioid Place Preference

A *meta*-analysis has been conducted on conditioned place preference studies with morphine and heroin (as well as cocaine and amphetamine) in rats, published between 1979 and 1992 (Bardo et al., 1995). The influence of a variety of experimental factors was analyzed. These included drug dose, route of administration, number of conditioning trials, trial duration, test duration, drug compartment, number of apparatus compartments, and use of intervening saline trials or a preconditioning test, as well as sex, strain, and housing conditions of the animals. The data revealed no consistent influence of the sex of the animals used. When the data were analyzed for strain effects, Sprague-Dawley and Wistar rats were found to be more sensitive to the place-conditioning effects of morphine and heroin than other strains. With regard to social circumstances, individual housing at the time of the experiment appeared to enhance the sensitivity for heroin-induced place-conditioning. It has, however, also been described that isolation rearing made rats less sensitive to the ability of morphine and heroin to establish conditioned place preference (Schenk et al., 1983, 1985; Wongwitdecha and Marsden, 1996). Indeed, it was recently shown that rats reared in enriched environments were more sensitive to morphine-induced place-conditioning than animals reared under impoverished circumstances, which included social isolation (Bardo et al., 1997). With respect to social status, dom-

inant animals seem to be more sensitive to the place-conditioning effects of morphine than their submissive counterparts (Coventry et al., 1997). There is, as yet, only one report on the effects on prenatal morphine treatment on place-conditioning. In that study, rats prenatally exposed to morphine appeared to be more sensitive to the place preference-inducing effects of morphine (Gagin et al., 1997). With respect to the effects of stress, it appeared that uncontrollable, but not escapable, footshock stress potentiated the effects of morphine on place-conditioning (Will et al., 1998).

Dose dependence was found for both morphine, with doses above 1 mg/kg generally producing place preference, and heroin, with doses above 0.3 mg/kg generally producing place preference. Although for heroin a relationship between drug dose and effect magnitude was found, such a relationship was much less clear for morphine. Regarding the route of administration, it was found that for morphine, s.c., as compared to i.p. and i.v., administration was slightly more effective. In the case of heroin, i.p. administration appeared to be much more effective than s.c. administration in inducing conditioned place preference. Regarding the number of conditioning trials, no clear picture emerged. This was due to the fact that in the case of morphine, a single i.v. administration had been reported to be effective in inducing conditioned place preference (Mucha et al., 1982; Bardo and Neisewander, 1986), whereas for heroin, only reports using three or four trials were available for analysis. In general, a longer conditioning trial duration (45 min or more for morphine, 25 min or more for heroin) appeared to be more effective, although in this case the analysis was quite complicated. For example, upon i.v. morphine administration, 10- or 90-min conditioning trials did not induce different levels of place preference (Mucha et al., 1982), whereas in the case of heroin, an inverted U-shaped relationship appears to exist: 10- or 100-min trials being less effective than 30-min trials (Bozarth, 1987a). With regard to experimental design, it also appeared that the test duration (10–30 min) had no marked influence on the expression of conditioned place preference. Counterbalanced administration of the conditioning drugs (as opposed to administering the drugs in the least preferred compartment in a biased design, or in the white compartment of a black-white apparatus) enhanced the strength of the place-conditioning, as did the use of saline trials in the nondrug-paired environment between conditioning trials (e.g., Scoles and Siegel, 1986). A preconditioning test, used to determine initial preference of the animal for a certain compartment of the test apparatus, negatively influenced morphine-induced place-conditioning. Finally, in the case of heroin, the use of a three-compartment apparatus yielded a more sensitive design than a two-compartment apparatus (Bardo et al., 1995).

1. Aversive Effects of Opioids. Morphine-induced place preference is considered to be mediated in the CNS.

However, aversive place-conditioning effects with morphine have also been reported. Studies by Van der Kooy and colleagues have indicated that stimulation of peripheral opioid receptors, especially in the gut, may be responsible for these effects. Low doses of morphine, when injected i.p., induced a place aversion that could be attenuated by peripheral administration of methylnaltrexone. This place aversion was absent in vagotomized rats. Likewise, place preference was found to result from i.p. injection of low doses of naltrexone or methylnaltrexone, which was also attenuated by vagotomy. In contrast, vagotomy did not influence place preference or aversion induced by i.p. injections of higher doses of morphine or naltrexone, respectively (Bechara and Van der Kooy, 1985; Bechara et al., 1987). The low doses of morphine and naltrexone used in the mentioned studies suggest that the peripheral aversive effects of opioids are mediated through μ receptors. There seems to be a role for κ receptors as well, since the place aversion induced by U50,488H could also be attenuated by vagotomy (Bechara and Van der Kooy, 1987). The dopaminergic innervation of the agranular insular cortex has been proposed as a central site in which the peripheral aversive effects of morphine are mediated. The place aversion elicited by i.p. injected low doses, but not the preference induced by higher doses of morphine, were blocked in rats with 6-OHDA-induced lesions of the agranular insular cortex (Zito et al., 1988).

2. Tolerance, Physical Dependence, and Sensitization. Pretreatment with morphine has been shown to decrease the ability of morphine to induce place preference, at least when place-conditioning was commenced shortly after pretreatment (Shippenberg et al., 1988a). This effect could indicate tolerance to the place-conditioning effects of morphine. However, residual morphine administered during pretreatment could also have interfered with morphine-induced place-conditioning. Interestingly, further training with morphine after conditioned place preference was established has been found, depending on the dose used, not to affect or even enhance the strength of place preference (Contarino et al., 1997). This suggests that during extensive training, no tolerance, but perhaps even sensitization to the rewarding effects of morphine, develops. In this study, during or after withdrawal from morphine treatment (10 conditioning trials with 10 mg/kg morphine), no overt signs of physical dependence were observed, suggesting that morphine-induced place preference can be elicited with doses lower than those necessary to induce physical dependence (Contarino et al., 1997).

The capacity of naloxone to induce conditioned place aversion appeared to be enhanced by nearly two orders of magnitude in rats previously implanted with a morphine pellet (Mucha et al., 1982). The enhanced ability of naloxone to induce a place aversion in morphine-withdrawn rats could even be observed 24 h after a single injection with morphine (20 mg/kg s.c.) (Parker and

Joshi, 1998). Place aversion induced by naltrexone in rats physically dependent on morphine appeared not to be associated with somatic signs of opioid withdrawal (Mucha, 1987). Indeed, in physically dependent rats, i.c.v. administration of methylnaloxonium induced a significant place aversion, whereas s.c. methylnaloxonium did not (Hand et al., 1988). Conversely, withdrawal from chronic treatment with naltrexone actually appeared to enhance morphine's properties to induce conditioned place preference (Bardo and Neisewander, 1987).

Research by Van der Kooy and colleagues has indicated a distinction between the place-conditioning effects of opioids in drug-naive and physically dependent animals. Briefly, morphine-induced place preference can be blocked by lesions of the tegmental pedunculopontine nucleus in drug-naive but not in physically dependent animals. In contrast, DA antagonists only abolished place preference (associated with relief of withdrawal) in physically dependent but not opioid-naive rats (Bechara and Van der Kooy, 1987; Bechara et al., 1992, 1995). These findings could account for the controversial results reported with respect to the role of mesolimbic DA in opioid place-conditioning (see *VIII. Addiction and Endogenous Opioids*), as this system might only come into play in the case of physical dependence. Interestingly, in the first report on morphine-induced place-conditioning that suggested an involvement of dopaminergic mechanisms in this phenomenon, rats physically dependent on morphine were used (Schwartz and Marchok, 1974). It has been suggested that even morphine administered intra-VTA (the effects of which are thought to be strictly dopaminergic) only induces DA-dependent place preference in physically dependent animals (Nader and Van der Kooy, 1997). The place preference induced by intra-VTA-administered morphine could, in drug-naive rats, be blocked by lesions of tegmental pedunculopontine nucleus, but not by treatment with a DA antagonist, suggesting a nondopaminergic substrate in the VTA associated with opioid-induced place-conditioning.

Although some of these are centrally mediated, the somatic signs of opioid withdrawal have been shown not to be responsible for opioid withdrawal-induced place aversion (Mucha, 1987; Hand et al., 1988). Thus, there has been some effort in finding the cerebral locus where this phenomenon might be mediated. Lesions of the dorsomedial amygdala, but not the NAC, were found to reduce the aversiveness of opioid withdrawal (Kelsey and Arnold, 1994). In view of the aforementioned studies by Van der Kooy and colleagues this is particularly interesting, since the dopaminergic cells in the VTA project to both NAC and amygdala. This suggests that the opioid-withdrawal associated morphine-induced place preference involves DA in the amygdala. However, Koob and colleagues demonstrated place aversions in physically dependent rats induced by methylnaloxone injections into the NAC, periaqueductal gray, and medial thalamus. Of these sites, the NAC was the most

sensitive site (Koob et al., 1989b; Stinus et al., 1990). Other studies have also shown that the mesolimbic DA system, as well as κ-opioid receptors, are involved in the aversiveness of morphine-withdrawal (Spanagel et al., 1994). With respect to receptor types involved in opioid withdrawal-induced place aversion, alongside μ- and κ-opioid receptors, δ receptors were also involved. Beside naloxone, the δ-opioid antagonists naltrindole and naltriben were capable of inducing place aversion in physically dependent rats (Funada et al., 1996).

Intermittent pretreatment with morphine has been shown to increase the ability of morphine and cocaine, but not of the selective DA reuptake inhibitor GBR-12783 to induce place preference (Lett, 1989; Gaiardi et al., 1991; Shippenberg and Heidbreder, 1995a; Spanagel, 1995; Shippenberg et al., 1996a, 1998; Greksch et al., 1998; Le Pen et al., 1998) to induce place preference. This indicates that morphine-induced behavioral sensitization, defined as an increased behavioral response to a given dose of drug or a response of a similar magnitude upon treatment with a lower dose of drug (Stewart and Badiani, 1993), is not only apparent with respect to its locomotor effects (Babbini and Davis, 1972; Babbini et al., 1975; Vanderschuren et al., 1997), but also its place-conditioning effects. Both morphine-induced locomotor sensitization and the sensitization to the place-conditioning effects are long-term phenomena, since sensitization of both can be found until at least 3 weeks post-treatment (Babbini and Davis, 1972; Babbini et al., 1975; Gaiardi et al., 1991; Shippenberg et al., 1996a; Vanderschuren et al., 1997).

In conclusion, by pretreating animals with opioids before place-conditioning, central systems responsible for the effects of opioid-induced place-conditioning can be modulated in such ways that animals will become more or less sensitive to the effects of opioids on place-conditioning. There is far more experimental evidence for the occurrence of sensitization than for opioid-induced tolerance to the effects of opioids on place-conditioning. In addition, if chronic stimulation of central opioid systems is ceased, the consequences of which can be enhanced by administration of an opioid antagonist, withdrawal-induced place aversion can be found.

VI. Endogenous Opioids and Nonopioid Drugs of Abuse

The discovery in the brain of opioid-binding sites and endogenous morphine-like substances (Pert and Snyder, 1973; Simon et al., 1973; Terenius, 1973; Hughes et al., 1975) has led to the hypothesis that opioid receptors may be sites where opioids agonists, such as morphine and heroin, induce, among others, opioid reinforcement and addiction. A role of endogenous opioids in the reinforcing and dependence-creating properties of opioids, but also of nonopioid drugs of abuse, has been proposed. In this section, the involvement of the endogenous opioids in reinforcement from and dependence on nonopioid

drugs will be discussed in more detail. The discussion will be focused on psychostimulants and ethanol, because available information on the role of endogenous opioids in reinforcement from other nonopioid drugs, such as nicotine, Δ^9-tetrahydrocannabinol, and benzodiazepines, is very limited.

A. Psychostimulants

In a human study with cocaine abusers, it was found that chronic treatment with the opioid antagonist naltrexone reduced euphoria and the "crash" from an i.v. cocaine injection (Kosten et al., 1992, but see Walsh et al., 1996). This finding suggests that the endogenous opioid system may be involved in certain aspects of cocaine addiction. Results from animal studies wherein the effect of opioid blockade on cocaine self-administration was studied generally seem to confirm such an involvement (for review, see Mello and Negus, 1996). In rats trained to i.v. self-administer cocaine, systemic pretreatment with the opioid antagonists naloxone or naltrexone dose-dependently (0.1–10 mg/kg s.c.) decreased cocaine self-administration, supposedly by a decrease of the reinforcing effects of cocaine (Corrigall and Coen, 1991). Similarly, daily treatment with naltrexone (0.32–3.2 mg/kg i.v.) decreased cocaine's reinforcing properties in monkeys (Mello et al., 1990). In another study, naltrexone was found to increase cocaine self-administration in trained rats, but only under certain conditions of food supply (Carroll et al., 1986a). The authors suggested that naltrexone either increased the reinforcing effects of cocaine, resulting in a higher cocaine intake, or decreased the reinforcing effects in which case more responding is needed to produce the same drug effect. Nonetheless, the study supports the existence of an effect of opioid blockade on cocaine self-administration. In contrast to the above-mentioned findings, other studies did not find a significant effect of naltrexone treatment on the rate or pattern of cocaine intake in rats and metamphetamine intake in rhesus monkeys (Harrigan and Downs, 1978b; Ettenberg et al., 1982; Hemby et al., 1996). Moreover, treatment with the pure opioid antagonist quadazocine failed to affect cocaine-reinforced responding in rhesus monkeys (Winger et al., 1992).

Beside pure opioid antagonists, mixed opioid agonist-antagonists are also able to antagonize the reinforcing effects of cocaine during self-administration. Daily and intermittent buprenorphine treatment (0.1–0.7 mg/kg i.v.) significantly suppressed cocaine self-administration by rhesus monkeys, even more potently than the pure opioid antagonist naltrexone (Mello et al., 1989, 1990, 1992, 1993b; Winger et al., 1992; Lukas et al., 1995). Similar effects of buprenorphine have been found in rhesus monkeys self-administering smoked cocaine and in rats and mice i.v. self-administering cocaine (Carroll et al., 1992; Comer et al., 1996; A. V. Kuzmin, M. A. F. M. Gerrits, E. E. Zvartau, J. N. Van Ree, unpublished data). Although the exact mechanisms by which buprenorphine reduces cocaine self-administration are un-

known, it has been suggested that the μ agonistic properties of buprenorphine are important for its interactions with cocaine. When buprenorphine and naltrexone were administered simultaneously, naltrexone significantly attenuated buprenorphine's suppressive effects on cocaine self-administration, probably through antagonism of the μ agonist component of buprenorphine (Mello et al., 1993c; A. V. Kuzmin, M. A. F. M. Gerrits, E. E. Zvartau, J. N. Van Ree, unpublished data). In addition, buprenorphine has κ antagonist effects, which might contribute to its suppressive effects on cocaine self-administration (Brown et al., 1991). Other mixed opioid agonists-antagonists, such as nalbuphine and butorphanol, also reduced cocaine self-administration in rhesus monkeys, but this effect was not selective since food self-administration also decreased in a dose-dependent manner (Winger et al., 1992; Mello et al., 1993a). In mice, treatment with butorphanol and nalbuphine decreased initiation of i.v. cocaine self-administration (A. V. Kuzmin, M. A. F. M. Gerrits, E. E. Zvartau, J. N. Van Ree, unpublished data). When tested against a scale of different cocaine unit doses, butorphanol produced a rightward shift in the unit dose-response curve for cocaine, indicating a decrease of the reinforcing effects of cocaine, whereas nalbuphine shifted the dose-response curve to the left. Coadministration of naloxone did not influence the effects of butorphanol, suggesting the involvement of κ receptors in this effect.

During the initiation phase of cocaine self-administration (i.e., in drug-naive animals), treatment with naltrexone (1 mg/kg) decreased cocaine intake in rats, presumably by an attenuation of the reinforcing effects of cocaine (De Vry et al., 1989a). This suppressive effect was found when a threshold dose of cocaine (0.16 mg/kg/inf) was used, but not when a higher cocaine unit dose was available. In fact, naltrexone caused a rightward shift in the dose-response curve for cocaine, indicating that cocaine is less reinforcing after opioid blockade. A similar shift in dose-response curve for cocaine has been observed in mice treated with naloxone (0.01–1.0 mg/kg) (Kuzmin et al., 1997a). That naltrexone treatment was effective within a critical cocaine unit dose range is supported by the finding that naltrexone decreased cocaine self-administration at unit doses of 0.1 and 0.3 mg/kg/inf, but not at 1.0 mg/kg/inf (Corrigall and Coen, 1991). The proposed involvement of opioid systems in the reinforcing effects of cocaine is also supported by the observation that chronic treatment with naltrexone (10 mg/kg/day for 12 days) followed by a naltrexone-free interval facilitated the initiation of cocaine self-administration, probably by enhancing the reinforcing effects of cocaine (Ramsey and Van Ree, 1990). Suppression of cocaine intake after i.c.v. administration of naltrexone suggests that naltrexone exerts its effect on initiation of cocaine self-administration through an action on the CNS (Ramsey and Van Ree, 1991). With regard to the local opioid systems in the brain, treat-

ment with naltrexone (1 μg/site) in the VTA, but not in the NAC, caudate putamen, central amygdala, or medial prefrontal cortex, attenuated cocaine self-administration behavior (Ramsey et al., 1999). Thus, opioid systems in the VTA may be implicated in modulating initiation of cocaine self-administration.

The above-mentioned effects on cocaine self-administration have been found after blockade with nonselective μ-opioid antagonists such as naloxone and naltrexone. Recently, the effects of more selective opioid ligands on the reinforcing effects of cocaine were studied. After a number of days of stable cocaine intake by rats, acute blockade of the δ-opioid receptor by naltrindole (3–10 mg/kg) reduced the self-administration of cocaine (0.4 mg/kg/inf) (Reid et al., 1995). In another study, naltrindole (0.03–10 mg/kg) failed to affect cocaine self-administration at unit doses of 0.25 and 1.0 mg/kg/inf in trained rats (De Vries et al., 1995). In rhesus monkeys trained to self-administer cocaine, treatment with the δ-opioid antagonist naltrindole (0.1–3.2 mg/kg) for 10 consecutive days decreased cocaine intake, although in some monkeys the response rate for cocaine recovered to baseline levels during the last days of naltrindole treatment (Negus et al., 1995). The reduction of cocaine intake seems to be dependent on the dose of cocaine offered, since naltrindole effectively decreased the self-administration of 0.01 mg/kg/inf cocaine, but was ineffective or less effective in decreasing the self-administration of either higher or lower unit doses of cocaine. Thus, naltrindole may modulate the reinforcing effects of cocaine, probably by blocking δ-opioid receptors. The involvement of κ-opioid receptors in cocaine reinforcement has also been demonstrated. Treatment with the selective κ-opioid agonists U50,488H and spiradoline dose-dependently decreased cocaine self-administration in rats (Glick et al., 1995, Kuzmin et al., 1997b). Although the κ antagonist nor-BNI had no effect on cocaine self-administration, it fully antagonized the effect of U50,488H (Glick et al., 1995). In monkeys, treatment with the κ agonists ethylketocyclazocine and U50,488H dose-dependently decreased cocaine self-administration of unit doses at the peak of the cocaine dose-effect curve (Negus et al., 1997). The effect of the κ agonist was blocked by the κ antagonist nor-BNI and naloxone and was accompanied by some undesirable effects. Interestingly, Kuzmin et al. (1997b) showed that treatment with U50,488H induced proper self-administration behavior with lower subthreshold unit doses of cocaine, doses that did not initiate self-administration under control conditions. In fact, the dose-response curve for cocaine reinforcement was shifted to the left, which may explain the observation of the decreased self-administration of cocaine by U50,488H when higher unit doses of cocaine were used (Glick et al., 1995, Kuzmin et al., 1997b). This latter finding suggests that activation of the κ-opioid systems increases the sensitivity for cocaine's reinforcing effects. Accordingly, the

κ-antagonist nor-BNI shifted the dose-response curve for cocaine reinforcement to the right. (Kuzmin et al., 1998). Thus, it seems that blockade of the μ-, δ-, or κ-opioid receptors, may make the animals less sensitive for cocaine reinforcement, whereas activation of κ-opioid receptors may result in the opposite. The results obtained so far stress the necessity of complete dose-response studies with respect to cocaine reinforcement before definitive conclusions are drawn.

Some internal and external factors affecting ICSS may use endogenous opioid systems. The potentiating effect of chronic food restriction on ICSS was reversed by naloxone and the μ antagonist TCTAP and the κ antagonist nor-BNI (Carr and Simon, 1984; Carr and Wolinsky, 1993; Carr and Papadouka, 1994). Also, the decrease in response rate of ICSS induced by inescapable footshock was antagonized by naloxone (Kamata et al., 1986). As already described before, drugs of abuse in general facilitate ICSS. The threshold-lowering effect induced by cocaine, amphetamine, or phencyclidine was reversed by naloxone treatment (Esposito et al., 1980; Kornetsky et al., 1981a,b.; Bain and Kornetsky, 1987; Van Wolfswinkel et al., 1988). Similar effects have been reported with respect to increase in response rate by amphetamine (Holtzman, 1974). Also, under the condition of a fixed interval schedule of reinforcement, naloxone attenuated the increase in response rate induced by amphetamine but not that by phencyclidine (Schaefer and Michael, 1990). The cocaine-induced facilitation of ICSS from the medial forebrain bundle was blocked by systemic treatment with the δ-opioid antagonist naltrindole (Reid et al., 1993). Thus, endogenous opioids may play a mediatory role for the effects of some drugs of abuse on ICSS.

Although the place preference induced by opioid drugs has amply been demonstrated to be mediated through opioid receptors, this has been shown for other drugs as well. In the case of cocaine, the development of conditioned place preference was prevented by coadministration of low doses of naloxone or naltrexone (Houdi et al., 1989; Suzuki et al., 1992b; Gerrits et al., 1995; Kim et al., 1997; Kuzmin et al., 1997a). Methadone appeared to enhance cocaine's place-conditioning effects, whereas the opioid mixed agonist-antagonist buprenorphine has been reported to both block and enhance cocaine-induced place preference conditioning (Brown et al., 1991; Kosten et al., 1991; Bilsky et al., 1992; Suzuki et al., 1992b). Apart from blocking the development, naloxone also blocked the expression of cocaine-induced conditioned place preference (Gerrits et al., 1995). The lowest effective doses of naloxone were 0.032 and 0.1 mg/kg s.c. for expression and development of cocaine-induced place preference, respectively (Gerrits et al., 1995).

δ-Opioid receptors have also been suggested to be involved in cocaine-induced place-conditioning, as naltrindole (nonspecific δ antagonist), naltriben (δ₂ antag-

onist), but not BNTX (δ_1 antagonist) appeared to block the development of cocaine-induced place preference (Menkens et al., 1992; Suzuki et al., 1994a). However, a detailed study on the influence of naltrindole reported no effect of naltrindole on cocaine-induced place-conditioning (De Vries et al., 1995). Recently, i.c.v. administration of an antisense oligodeoxynucleotide to δ receptors was found to inhibit cocaine-induced place preference (Suzuki et al., 1997b). The κ agonist U50,488H could also block cocaine-induced place preference (Suzuki et al., 1992b; Crawford et al., 1995). In addition to attenuating cocaine-induced place preference, naloxone, naltrindole, and naltriben also blocked amphetamine-induced place preference (Trujillo et al., 1991; Suzuki et al., 1994a). Similar to morphine pretreatment (see *V. Tolerance, Physical Dependence, and Sensitization*), pretreatment with cocaine has been shown to induce sensitization to the place-conditioning effects of cocaine and morphine in rats. This sensitization induced by preexposure to cocaine could be attenuated by coadministration of the δ antagonist naltrindole and the κ agonist U50,488H or U69,593 (Shippenberg and Heidbreder, 1995a,b; Shippenberg et al., 1996b, 1998; Shippenberg and Rea, 1997). Remarkably, the sensitization of the place-conditioning effects of morphine and cocaine induced by morphine pretreatment could not be attenuated by U69,593 coadministration (Shippenberg et al., 1998).

Thus, stimulation of opioid receptors seems to be involved in psychostimulant-induced place-conditioning. The involvement of δ-opioid receptors is not undebated, but the low doses of naloxone and naltrexone sufficient to inhibit cocaine- and amphetamine-induced place-conditioning suggest a prominent role for μ receptors. In addition, δ- and κ-opioid receptors seem to be involved in the cocaine-induced sensitization to the place-conditioning effects of cocaine.

Studying the neostriatum of human subjects with a history of cocaine dependence, it was found that cocaine dependence was linked with selective alterations in striatal opioid mRNA expression and opioid receptor binding (Hurd and Herkelham, 1993). Reductions in the levels of enkephalin mRNA and μ-opioid receptor binding were found in the striatum concomitant with elevations in levels of dynorphin mRNA and κ-opioid receptor binding. Using positron emission tomography, it was found that μ-opioid receptor binding was increased in several brain regions of cocaine addicts (Zubieta et al., 1996). The change in binding was positively correlated with the degree of cocaine craving the addicts experienced. In cocaine overdose addicts, an increase in κ_2-opioid receptors was found in the NAC and amygdala (Staley et al., 1997). Although the functional relationship between these alterations and cocaine dependence is not clear, this finding provides neurochemical evidence for an involvement of endogenous opioid systems in cocaine dependence.

A number of studies have investigated the effect of administration of psychostimulants in rats on the levels of endogenous opioids, expression of opioid mRNA and opioid receptors in the brain (for review, see Trujillo et al., 1993). Investigations on the action of psychostimulant drugs on the β-endorphin system are limited. It has been reported that acute and chronic treatment with cocaine induced an increase in levels of βE-IR in plasma and pituitary (Moldow and Fischman, 1987; Forman and Estilow, 1988). Furthermore, chronic treatment with cocaine induced an increased release of β-endorphin from the pituitary in vitro (Forman and Estilow, 1988). No effect of chronic treatment with cocaine and amphetamine on the levels of βE-IR in the hypothalamus were found (Harsing et al., 1982; Agarwal et al., 1985; Forman and Estilow, 1988).

Reports on the enkephalin system are consistent in demonstrating a lack of effect of acute and chronic treatment with psychostimulants on enkephalin immunoreactivity in the striatum and in other brain structures such as cortex, hippocampus, hypothalamus, and brain stem (Harsing et al., 1982; Sivam, 1989; Li et al., 1990; Trujillo et al., 1990). In contrast to a lack of effect on levels of enkephalin peptides in the brain, acute cocaine and metamphetamine increased the expression of enkephalin mRNA in the striatum and amygdala (Bannon et al., 1989; Cohen et al., 1991; Hurd et al., 1992; Wang and McGinty, 1995). Subchronic or chronic treatment did not, however, affect the enkephalin mRNA expression (Sivam, 1989; Branch et al., 1992; Daunais and McGinty, 1994). The correlation between changes in expression of enkephalin mRNA and levels of enkephalin peptides needs, however, to be elucidated, including its relevance for cocaine reinforcement and dependence.

The effect of acute administration of psychostimulants, such as cocaine, amphetamine, and metamphetamine, on the dynorphin system has been examined extensively, and the results are equivocal. The investigations have primarily been focused on the striatonigral dynorphin system. Summarizing, acute administration of psychostimulants increased, decreased, or had no effect on dynorphin immunoreactivity levels in the striatum and/or substantia nigra (Peterson and Robertson, 1984; Hanson et al., 1988; Li et al., 1988; Sivam, 1989; Trujillo et al., 1990; Johnson et al., 1991; Singh et al., 1991). Moreover, acute treatment increased or did not affect the expression of dynorphin mRNA in the striatum and NAC (Hurd et al., 1992; Daunais and McGinty, 1994; Wang and McGinty, 1995). More consistent effects were found after subchronic or repeated treatment with psychostimulants; increased striatal levels of dynorphin immunoreactivity and dynorphin mRNA levels have been reported (Peterson and Robertson, 1984, Li et al., 1986, 1988; Hanson et al., 1987, 1988, 1989; Sivam, 1989; Trujillo and Akil, 1989, 1990; Smiley et al., 1990; Trujillo et al., 1990; Gerfen et al., 1991; Hurd et al., 1992; Steiner and Gerfen, 1993; Daunais and McGinty,

1994; Smith and McGinty, 1994). In addition, increased dynorphin levels were demonstrated in the substantia nigra, NAC, but not hippocampus (Sivam, 1989; Smiley et al., 1990; Trujillo et al., 1990).

Studies on animals self-administering cocaine shed some more light on the potential involvement of β-endorphin in processes underlying cocaine dependence. Sweep et al. (1988, 1989) found marked decreases in βE-IR levels in the anterior part of the limbic system (i.e., NAC, septum, hippocampus, and rostral striatum) in animals self-administering cocaine. Furthermore, using an in vivo autoradiographic technique, a decrease in opioid receptor occupancy was found in restricted subcortical brain regions of animals self-administering cocaine, including limbic areas (i.e., lateral septum, ventral pallidum, nucleus stria terminalis, and amygdala) and some regions of the hypothalamus and thalamus (Gerrits et al., 1999). The decrease in opioid receptor occupancy is probably due to a release of endogenous opioids in these particular brain regions. Interestingly, both of these changes (i.e., decreased βE-IR content and increased endogenous opioid release) were present just before a scheduled next cocaine self-administration session would have taken place; thus, when the desire or need for the drug is assumed to be high. This might suggest an involvement of endogenous opioids, and possibly β-endorphin, in the processes underlying the need for cocaine. When the same methodologies were used in rats that just had completed their daily cocaine self-administration session, it appeared that βE-IR levels in the brain were hardly changed and that a decrease of opioid receptor occupancy was present in many brain areas, including the NAC (Sweep et al., 1988; Gerrits et al., 1999). Daunais et al. (1993), investigating the effect of cocaine self-administration on the expression of dynorphin mRNA, found an increased expression in the patch-like areas of the dorsal, but not in those of the ventral, striatum. Because repeated high doses of cocaine given for 6 to 7 days were necessary to induce this effect, the authors concluded that the increased dynorphin mRNA expression does not underlie the acute reinforcing effects of cocaine but is more associated with long-term adaptation and sensitization.

Besides regulating the level of endogenous opioids and the expression of opioid mRNA in the brain, studies have demonstrated that psychostimulant drugs also regulate the density of opioid receptors in the brain. Chronic cocaine exposure reduced opioid receptor density, as labeled by [³H]naloxone, in the hippocampus and striatum and in the basolateral nucleus of the amygdala, VTA, substantia nigra, and dorsal raphe nuclei (Ishizuka et al., 1988; Hammer, 1989). An increase in opioid receptor density was found in the NAC, ventral pallidum, and lateral hypothalamus. In light of the selective opioid receptors in the brain, studies were performed with more selective radioligands. In short, chronic treatment of rats with cocaine caused an up-regulation of μ-opioid

receptors in the cingulate cortex, NAC, rostral caudate putamen, and basolateral amygdala; an up-regulation of κ-opioid receptors in the cingulate cortex, rostral caudate putamen, olfactory tubercle, and VTA; and no change in δ-opioid receptors in any of the brain regions examined (Unterwald et al., 1992, 1994). Itzhak (1993), studying the effect of chronic cocaine treatment on opioid receptor densities in guinea pigs, found a significant down-regulation of μ-opioid receptors in frontal cortex, amygdala, thalamus, and hippocampus; an alteration in the expression of κ-opioid receptors in the cerebellum; and no significant changes in δ-opioid receptor expression. Furthermore, it was shown that "binge" pattern of cocaine administration led to significant decreases in the level of κ-opioid receptor mRNA in the substantia nigra but not in the caudate putamen (Spangler et al., 1997). Finally, to determine the functional consequences of chronic cocaine on opioid receptors, Unterwald et al. (1993) measured changes in adenyl cyclase activity. They found that chronic cocaine administration resulted in a selective impairment of δ-opioid receptor-mediated function in the caudate putamen and NAC.

In conclusion, a role for μ-opioid receptors and β-endorphin in cocaine dependence seems likely. This role may be at the level of modulating the reinforcing action of cocaine and the motivational state induced by repeated cocaine exposure. Concerning the κ- and δ-opioid receptors and the dynorphin and enkephalin systems, the data so far do not allow definitive conclusions. In particular, it is not clear how to link effects of passive administration of cocaine with the addiction, e.g., self-administration process.

B. Ethanol

In 1970, a biochemical link was proposed between ethanol and opioid systems based on the finding that condensation of the ethanol metabolite acetaldehyde and biogenic amines produced tetrahydroisoquinolines (TIQs). These TIQs seemed to have opioid-like effects (Davish and Walsh, 1970; Cohen and Collins, 1970; Fertel et al., 1980). Long-term ethanol self-administration induced the formation of TIQs in the brain of rats (Collins et al., 1990; Haber et al., 1996). Furthermore, TIQs induced excessive alcohol drinking, an effect that was modulated by morphine and naloxone (Critcher et al., 1983). Evidence for an involvement of the endogenous opioid systems in ethanol reinforcement and addiction is provided by studies with opioid antagonists and agonists (for reviews, see Herz, 1997; Spanagel and Zieglsgängsberger, 1997).

Opioid antagonists, such as naltrexone and naloxone, decrease ethanol self-administration in rodents and monkeys under a variety of different experimental conditions. Although opioid blockade by antagonists blocked intragastric (Sinden et al., 1983) and i.v. (Altshuler et al., 1980; Martin et al., 1983) self-administration of ethanol, the majority of studies on the involvement of en-

dogenous opioids in ethanol reinforcement have used an oral self-administration paradigm. Altshuler et al. (1980), using rhesus monkeys experienced with alcohol intake, found that chronic treatment with naltrexone (1–3 mg/kg i.m.) on a daily basis for 15 days dose-dependently decreased i.v. ethanol administration by as much as 50%. A later study with alcohol-drinking rhesus monkeys supported this finding in that the total oral ethanol intake was reduced by acute treatment with naltrexone in a graded dose-dependent manner (0.02–1.5 mg/kg i.m.). The consumption of drinking water was much less affected by naltrexone (Kornet et al., 1991). Using different variants of ethanol-water choice procedures, treatment with low doses of naloxone (0.1–1 mg/kg) selectively and dose-dependently decreased the preference for ethanol in rats (De Witte, 1984; Sandi et al., 1988; Schwartz-Stevens et al., 1992). Evidence has been presented that the amount of ethanol intake could be decreased without altering the water intake. Furthermore, the decrease in ethanol intake was found to be independent of palatability of the presented alcohol (i.e., alcohol mixed with saccharin or quinine). A lack of blockade of ethanol intake by the peripherally acting opioid antagonist methylnaltrexone indicates a central site of action of opioid blockade of ethanol intake (Linseman, 1989). A number of other reports confirmed the decreasing effect of opioid antagonists on ethanol intake (e.g., Marfaing-Jallat et al., 1983; Reid and Hunter, 1984; Samson and Doyle, 1985; Hubbell et al., 1986, 1991; Mason et al., 1993; Froehlich, 1995; Ulm et al., 1995; Davidson and Amit, 1996).

The effect of opioid blockade was found in nondeprived animals and during conditions of continuous and concurrent supply, but has also been investigated in alcohol-abstinence studies. In rhesus monkeys who had about 1 year of experience with alcohol drinking, short and longer periods of imposed interruptions of alcohol supply (up to 7 days) led to a temporary increase in ethanol intake ("catch-up" phenomenon) and a subsequent relapse in the preinterruption drinking habit (Kornet et al., 1990). Blockade of opioid receptors with naltrexone after 2 days of imposed abstinence dose-dependently reduced the abstinence-induced increase in ethanol intake after renewed presentation of ethanol (Kornet et al., 1991). Interestingly, a lower dose of naltrexone (0.17 mg/kg i.m.) was effective in reducing ethanol intake after imposed abstinence as compared to during continuous supply of alcohol, suggesting a role for endogenous opioids in the catch-up phenomenon (Kornet et al., 1991). Reid et al. (1991) used a different regimen of imposed abstinence in rats involving 22 h of deprivation of fluids followed by 2 h of access to water and a sweetened ethanol solution. Treatment with naloxone (4 mg/kg) 30 min before a day's opportunity to take fluids decreased the intake of ethanol, whereas an injection with naloxone 4 h before alcohol supply increased ethanol intake. Taken together, the results from the studies with opioid blockade suggest an involvement of endogenous opioids in ethanol reinforcement.

The effect of more selective opioid receptor antagonists on ethanol intake has mostly been studied in selectively bred strains of high alcohol-drinking or -preferring rats (for review, see Froehlich, 1995). In these rat strains [e.g., high alcohol drinking (HAD) and the alko alcohol (AA)], treatment with the nonselective opioid antagonists naloxone and naltrexone dose-dependently decreased voluntary oral ethanol intake (Pulvirenti and Kastin, 1988; Froehlich et al., 1990; Hyytiä and Sinclair, 1993; Myers and Lankford, 1996). The selective μ-opioid antagonist CTOP, administered i.c.v., significantly decreased ethanol intake in AA rats. In the same rat strain, selective blockade of the δ-opioid receptor with ICI 174,864 or naltrindole had no effect on alcohol drinking (Hyytiä, 1993; Honkanen et al., 1996). Contrary to these findings, ICI 174,864 and naltrindole significantly decreased ethanol consumption as efficiently as naloxone in the high-drinking HAD rats (Froehlich et al., 1991; Froehlich, 1995). ICI 174,864 and naltrindole also suppressed ethanol intake in another rat strain with high alcohol preference (P-line). This effect of naltrindole was, however, not specific for ethanol, as evidenced by the fact that naltrindole reduced intake of saccharin solutions with and without ethanol (Krishnan-Sarin et al., 1995a). Furthermore, naltriben, an antagonist selective for the δ_2-opioid receptor, suppressed ethanol intake in rats of the P-line (Krishnan-Sarin et al., 1995b). This effect appeared to be specific for ethanol and independent of alcohol palatability. The involvement of μ- and δ-opioid receptors in ethanol reinforcement has also been investigated in the alcohol-preferring C57BL/6 mice. Naltrexone reduced ethanol intake in these mice, but the effect waned at increasing doses of naltrexone. Furthermore, chronic naltrexone treatment stimulated ethanol intake (Phillips et al., 1997). Administration of naltrindole decreased ethanol intake, but blockade of the μ-opioid receptor with β-funaltrexamine in these mice had no effect on alcohol consumption (Dzung et al., 1993). These data may suggest that in the AA rats the μ-opioid receptor is important in mediating ethanol reinforcement and in the HAD and P-line rats and C57BL/6 mice, the δ-opioid receptor. The effects of naltrexone and selective opioid receptor antagonists on ethanol consumption have also been studied in the Wistar rats (Stromberg et al., 1998). Naltrexone and the μ-selective opioid antagonist β-funaltrexamine significantly decreased the intake of an ethanol solution using a limited access procedure. Blockade of the δ-opioid receptor with naltrindole failed to significantly reduce ethanol consumption. These data suggest that in the outbred rat the μ-opioid receptor rather than the δ-opioid receptor is involved in ethanol reinforcement.

Bremazocine was found to potently suppress ethanol drinking in rats in a free-choice unlimited access model. The effect of bremazocine, which combines agonism at

κ receptors and the μ-δ receptor complex, with antagonistic actions at μ receptors (Heijna et al., 1989; Schoffelmeer et al., 1992) was not secondary to effects on motor activity or fluid intake. In addition, bremazocine did not affect intake of a highly preferred sucrose solution. Both naltrexone and the κ agonist U50,488H had only modest and transient suppressant effects on ethanol drinking, suggesting a role of the μ-δ receptor complex in the effect of bremazocine (Nestby et al., 1999). Buprenorphine, was found to reduce i.v. ethanol self-injection in rats and oral ethanol intake in rhesus monkeys (Martin et al., 1983; Carroll et al., 1992). In the latter study, buprenorphine, however, also attenuated saccharin-maintained responding.

The involvement of endogenous opioid systems in ethanol consumption has also been studied using opioid agonists. However, the results with opioid agonists are less consistent than those with opioid antagonists. In general, low doses of morphine stimulated ethanol intake in animals (Reid and Hunter, 1984; Hubbell et al., 1986, 1987, 1993; Reid et al., 1991), whereas moderate to high doses of morphine have been reported to suppress alcohol consumption (Sinclair et al., 1973; Sinclair, 1974; Ho et al., 1976; Czirr et al., 1987; Linseman, 1989; Volpicelli et al., 1991; Schwartz-Stevens et al., 1992). An increase in ethanol intake after i.c.v. administration of morphine indicated that the low-dose effect of morphine is centrally located (Linseman and Harding, 1990). Some unclarity about the low-morphine dose effect exists since other studies showed that low doses of morphine hardly affected or decreased ethanol intake in rats and monkeys, respectively (Kornet et al., 1992b; Schwartz-Stevens et al., 1992).

Measuring the preference for alcohol, Volpicelli et al. (1991) demonstrated that morphine lowered alcohol preference. The suppression of alcohol preference was related to the dose in that a high dose of morphine suppressed alcohol preference more than a low dose of morphine. Similar impairments in the acquisition of alcohol preference were reported after systemic administration of endogenous opioids such as β-endorphin, Leu-enkephalin, and a synthetic analog of Met-enkephalin (Sandi et al., 1989, 1990a,b). Using a daily abstinence regimen of 22 h of deprivation and 2 h of access to fluids, a low dose of morphine administered 30 min before the daily opportunity to drink fluids increased the intake of ethanol, whereas morphine administered 4 h before renewed alcohol supply decreased alcohol drinking (Reid et al., 1991). Furthermore, it has been shown that morphine enhanced ethanol place preference (Marglin et al., 1988). The development of ethanol-induced place aversion in rats was enhanced by naloxone, whereas naloxone did not influence the expression of ethanol-induced place aversion (Bormann and Cunningham, 1997).

Based on, among others, the above-mentioned preclinical studies wherein opioid antagonists reliably reduce alcohol consumption under a variety of circumstances,

clinical studies have been undertaken to assess the effect of naltrexone treatment in alcoholics. During a 12-week, double-blind, placebo-controlled trial, alcohol-dependent patients were treated with naltrexone-hydrochloride (50 mg/day) in adjunct to psychosocial treatment following alcohol detoxification. Subjects taking naltrexone reported significantly less alcohol craving. The number of days in which alcohol was consumed was significantly decreased by naltrexone and relapse was reduced. Of the placebo-treated patients, 95% relapsed after they drank alcohol again, whereas only 50% of the naltrexone-treated patients exposed to alcohol relapsed (Volpicelli et al., 1992). Additionally, a majority of the naltrexone-treated patients reported that the "high" produced by alcohol was significantly less than usual (Volpicelli et al., 1995c). These findings were replicated and extended by O'Malley et al. (1992, 1996) who, in addition, found that the reducing effects of naltrexone on alcohol drinking, craving, and relapse interacted with the type of supportive therapy the patients received. Naltrexone has recently received approval for the treatment of relapse in alcohol dependence, and thereby may offer a new treatment regimen in combination with psychosocial therapy to reduce relapse following alcohol detoxification (O'Malley, 1995; Swift, 1995; Volpicelli et al., 1995a,b). Another opioid antagonist, nalmefene, also has been reported to reduce alcohol consumption and to prevent relapse (Mason et al., 1994). Furthermore, naltrexone increased the latency to drink alcohol in social drinkers (Davidson et al., 1996, but see Doty and De Wit, 1995). The interaction between naltrexone and the subjective alcohol response seemed to depend on the degree of being at risk for alcoholism (King et al., 1997).

A possible involvement of endogenous opioids in alcohol addiction is supported by an early study demonstrating a 3-fold lower level of β-endorphin in the cerebrospinal fluid of abstinent, chronic alcohol addicts as compared with controls (Genazzani et al., 1982). Over the years, the interaction between ethanol and the activity of endogenous opioid systems and its possible implication for ethanol reinforcement and dependence have been studied in animals, but the results of these studies have not yielded an unified theory about the role of endogenous opioids in ethanol dependence (for overview and details, see Gianoulakis, 1989; Froelich and Li, 1993; Gianoulakis, 1993; Trujillo et al., 1993; Tabakoff et al., 1996).

Studies examining the effect of ethanol on the β-endorphin system have shown a variety of effects on brain β-endorphin. Acute treatment with ethanol increased, decreased, or had no effect on β-endorphin content in the pituitary and hypothalamus (Schultz et al., 1980; Seizinger et al., 1983; Wilkinson et al., 1986; Patel and Pohorecky, 1989; Przewlocka et al., 1990). An increased in vivo release of β-endorphin from the pituitary and hypothalamus after acute ethanol has been demonstrated (Gianoulakis and Barcomb, 1987). With regard

to chronic ethanol administration, also decreases, increases, or no effects on the β-endorphin levels were found in the pituitary and hypothalamus (Schultz et al., 1980; Cheng and Tseng, 1982; Seizinger et al., 1983). Similar discrepancies have been found for the effects of ethanol exposure on β-endorphin content in other brain regions (Schultz et al., 1980; Seizinger et al., 1983; Wilkinson et al., 1986; Przewlocka et al., 1990). Such inconsistencies were also found for the effects of ethanol exposure on brain content of enkephalin and dynorphin peptides and on the expression of opioid receptors in the brain (see Gianoulakis, 1989, 1993; Froehlich and Li, 1993; Trujillo et al., 1993). The discrepancy in ethanol-induced effects are in part due to differences in procedural variables (i.e., animal species examined, dose, route and duration of ethanol administration, areas of the brain examined, and whether ethanol-induced changes in opioid peptides were examined during or after ethanol administration). A different approach to study the link between endogenous opioids and ethanol reinforcement is the examination of strains of mice with different genetic propensities to drink alcohol. For example, Gianoulakis and Gupta (1986) demonstrated that the hypothalamic β-endorphin level was about 25% lower in the alcohol-nonpreferring DBA/2 mice as compared with the alcohol-preferring C57BL/6 mice. Moreover, the β-endorphin content in the hypothalamus decreased in the C57BL/6 mice in response to acute injection of ethanol but not in the DBA/2 mice. Additional studies showed that in C57BL/6 mice ethanol induced an enhanced in vitro release of hypothalamic β-endorphin, lower levels of β-endorphin in the NAC under basal conditions, and an increase in hypothalamic content of POMC-mRNA after 3 weeks of ethanol consumption (De Waele and Gianoulakis, 1993, 1994). Comparing alcohol-preferring AA and alcohol-avoiding ANA lines of rats, differences in the density of both μ- and δ-opioid receptors in distinct brain regions and in the dynorphin and enkephalin levels in the NAC were found (Nylander et al., 1994; De Waele et al., 1995). For a detailed discussion of genetically determined differences in the opioid system, we refer to the reviews of Gianoukalis and coworkers (Gianoukalis and De Waele, 1994; Gianoukalis et al., 1996). Subjects at high risk for alcoholism showed an increase in plasma levels of βE-IR upon administration of moderate doses of ethanol, whereas subjects at low risk did not respond in this way (Gianoukalis et al., 1996). In monkeys, differential effect on plasma β-endorphin levels in relation to the increase in alcohol consumption during initiation of alcohol self-administration has been reported (Kornet et al., 1992a). Alcoholism was accompanied by increased [³H]naloxone binding in several brain regions, particularly the frontal cortex (Ritchie and Noble, 1996). Thus, the genetic makeup of the endogenous opioid systems as well as the interaction between alcohol and these systems may contribute to the development of alcoholism.

There seems to be agreement on the assumption that ethanol drinking or administration stimulates the activity of the endogenous opioid systems that serves to reinforce further alcohol drinking and, in time, leads to the development of ethanol dependence. Two theories have been developed that focus on basal endogenous opioid activity as a "predisposing factor" for alcohol drinking and abuse. One theory, the "opioid deficit" or "opioid compensation" hypothesis predicts that a deficiency in endogenous opioids leads to alcohol-craving and increased alcohol-drinking (Blum, 1983; Erickson, 1990; Ulm et al., 1995). This theory assumes that because ethanol stimulates activity within the opioid system, ethanol is consumed to compensate for low basal levels of endogenous opioids. The other theory, the "opioid surfeit hypothesis" assumes that an excess of opioid activity leads to alcohol-craving and increased alcohol intake which is then reinforced by further ethanol-induced increases in opioid activity that culminates in ethanol dependence (Hunter et al., 1984; Reid et al., 1991). Little experimental evidence exists to substantiate either theory, but most findings so far can be best explained in the context of the opioid compensation hypothesis. That is, during conditions of excess opioid receptor activity, e.g., after treatment with morphine, alcohol consumption decreases. In contrast, during conditions with a deficiency in opioid activity, consumption of alcohol increases. A condition with a deficiency in opioid activity could be imposed abstinence. Short and longer periods of imposed interruptions of ethanol supply lead to a temporary increase in ethanol intake and a subsequent relapse in preinterruption drinking habit (Kornet et al., 1990). Blockade of opioid receptors with low doses of naltrexone reduced the abstinence-induced increase in ethanol intake, suggesting that craving and relapse are opioid-mediated (Kornet et al., 1991). A recent observation using an in vivo opioid receptor occupancy technique, showing that endogenous opioids were released in some limbic brain regions, i.e., the amygdala, hippocampus, ventral pallidum, nucleus stria terminalis, when the desire for ethanol is high in contrast to when the desire is probably low, agrees well with this hypothesis (Gerrits et al., 1999). In addition, it corroborates with recent findings in human alcoholics demonstrating that craving and relapse are attenuated after treatment with the opioid antagonist naltrexone (O'Malley et al., 1992; Volpicelli et al., 1992). Furthermore, some clinical evidence is available for an inverse relationship between alcohol and opiate use in heroin addicts (see Ulm et al., 1995).

VII. Brain DA and Opioid Drugs of Abuse

Among the brain substances and systems implicated in reinforcement and dependence, most attention is given to DA and the mesocorticolimbic DA system. The DA hypothesis of dependence is based, among others, on the reinforcing and dependence-creating properties of

drugs that enhance dopaminergic function (e.g., amphetamine and cocaine) and on the involvement of DA in ICSS (Wise, 1978, 1987, 1996; Di Chiara and Imperato, 1988; Wise and Rompré, 1989; Di Chiara and North, 1992; Koob, 1992).

Opioids have the ability to increase DA release in the NAC, a terminal area of the mesocorticolimbic DA system. This action has been suggested to be related to their reinforcing and dependence-creating properties. Additional evidence for an involvement of DA in the reinforcing effects of opioids comes from the finding that animals will press a lever to receive injections of opioids directly into the VTA, wherein the cell bodies of the mesocorticolimbic DA system are located (Van Ree and De Wied, 1980; Bozarth and Wise, 1981b; Welzl et al., 1989). Moreover, injection of opioids into the VTA increased DA release in the NAC (e.g., Leone et al., 1991; Rada et al., 1991). Together, these findings suggest that opioids can activate opioid receptors located in the VTA, which stimulates the ascending mesocorticolimbic DA system (e.g., the NAC), by which opioid reinforcement may be mediated. In the succeeding paragraphs, the role of brain DA in the effects of opioids is discussed on the basis of results with the self-administration, ICSS, and conditioned place preference models (for reviews, see Wise and Bozarth, 1982; Wise, 1989, 1996; Ramsey and Van Ree, 1992; Unterwald and Kornetsky, 1993).

Under maintenance conditions of i.v. self-administration, systemic treatment with the DA antagonists α-flupenthixol or pimozide only slightly decreased responding for i.v. heroin, whereas significant increases in cocaine self-administration, performed on alternating days, were observed (Ettenberg et al., 1982; Gerber and Wise, 1989). Similarly, treatment with haloperidol produced little or no effect on responding for heroin at doses that produced robust effects on cocaine self-administration (Higgins et al., 1994a). In other studies, however, heroin self-administration was attenuated by systemic treatment with neuroleptics (Glick and Cox, 1975; Davis and Smith, 1983; Van Ree and Ramsey, 1987), by the DA D2 antagonist eticlopride (Hemby et al., 1996), and by the selective DA D1 antagonist SCH23390 (Nakajima and Wise, 1987; Gerrits et al., 1994; Awasaki et al., 1997). However, all types of drugs were in general effective only at doses that also affect motor functioning or rate of responding, which questions the specificity of the observed effects. Moreover, chronic treatment with the neuroleptic flupentixol potentiated initiation of i.v. heroin self-administration (Stinus et al., 1989).

With regard to central loci involved in opioid self-administration, initiation of i.v. heroin self-administration was not altered by injection of relatively high doses of haloperidol into several brain regions which contained terminals of DA systems, including the NAC, amygdala, caudate putamen, medial prefrontal cortex, and pyriform cortex (Van Ree and Ramsey, 1987). The doses of haloperidol used were much higher than those needed to

antagonize effects of the DA agonist apomorphine locally applied in the mentioned brain regions (Van Ree et al., 1989), indicating that in the self-administration experiment sufficient DA blockade was attained. Administration of the DA D1 antagonist SCH23390 in the NAC also had no effect on heroin self-administration, yet decreased motor behavior, suggesting that DA D1 receptors in the NAC are not critically involved in initiation of heroin self-administration (Gerrits et al., 1994). Some research groups demonstrated that destruction of DA cell bodies in the VTA (Bozarth and Wise, 1986) and of the DA terminals in the central medial NAC (Smith et al., 1985) affected morphine intake during the maintenance phase of self-administration, whereas others reported that lesion of DA terminals in the NAC with 6-OHDA did not significantly affect initiation and maintenance of heroin self-administration (Pettit et al., 1984; Singer and Wallace, 1984; Dworkin et al., 1988a; Gerrits and Van Ree, 1996). Taken together, DA receptor blockade and destruction of DA terminals in the NAC do not indicate an important role of DA in this brain area in opioid reinforcement.

Reinstatement of lever-pressing in animals trained to i.v. self-administer heroin was obtained when morphine was injected into the VTA but not in the NAC (Stewart, 1984; Stewart et al., 1984). On the other hand, amphetamine injected into the NAC induced reinstatement (Stewart and Vezina, 1988). The DA agonist bromocriptine and the selective DA reuptake blocker GBR-12909 but not the direct DA agonists SKF 82958 (D1), quinpirole (D2), or apomorphine were also shown to induce reinstatement upon systemic administration, suggesting that DA systems per se are involved in this phenomenon (Stewart and Vezina, 1988; Wise et al., 1990; De Vries et al., 1999). Using in vivo microdialysis, an increase in extracellular DA levels in the NAC during and after i.v. heroin self-administration has been reported (Wise et al., 1995; M. A. F. M. Gerrits, P. Petromilli, H. G. M. Westenberg, G. Di Chiara, J. M. Van Ree, unpublished data). Also, DA-associated electrochemical signals in the NAC of animals allowed to self-administer heroin were elevated as compared to saline controls (Kiyatkin et al., 1993). On the other hand, others failed to find significant changes in extracellular DA in the NAC during i.v. heroin self-administration (Hemby et al., 1995). Measuring the activity of presumed DA neurons in the VTA, it was observed that these neurons are activated before the heroin injection, which was followed by an inhibition of activity due to the actual heroin injection (Kiyatkin and Rebec, 1997). In comparison, the extracellular DA concentration in the NAC, as measured with in vivo electrochemistry, decreased immediately after a lever press reinforced by heroin and gradually increased, reaching a peak at the moment of the next lever press (Kiyatkin, 1995). Finally, changes in basal levels of DA in the NAC in animals repeatedly exposed to sessions with heroin self-administration have been

found using in vivo microdialysis. That is, a 50% decrease of the basal DA levels in the NAC shell of animals self-administering heroin was observed (M. A. F. M. Gerrits, P. Petromilli, H. G. M. Westenberg, G. Di Chiara, J. M. Van Ree, unpublished data).

Opioids facilitate ICSS and the VTA is a sensitive site for these substances in this respect (see *IV. Effects of Opioids*). Since mesocorticolimbic DA has been implicated in ICSS, some studies have been performed to analyze the interaction between opioids and DA agonists and antagonists using ICSS. Low doses of the DA agonist *d*-amphetamine potentiated the facilitating effect of morphine on thresholds for ICSS, indicated by a leftward shift in the morphine dose-response curve (Hubner et al., 1987). Also, the more selective DA agonist amfonelic acid potentiated the effects of morphine and even to a greater extent than *d*-amphetamine (Izenwasser and Kornetsky, 1989). A combination of morphine and the DA antagonist pimozide blocked the threshold-lowering effects of morphine on ICSS (Rompré and Wise, 1989). In addition, a low dose of apomorphine, presumably acting at presynaptic DA receptors, blocked the morphine's ICSS threshold-lowering effects (Knapp and Kornetsky, 1996). The lowering of ICSS threshold by intra-NAC injections of the μ and δ agonists DAMGO and DPDPE, respectively, was blocked by the DA antagonist *cis*-flupenthixol (Duvauchelle et al., 1997). Although these studies may suggest an involvement of DA in the morphine-induced facilitation of ICSS, more studies are needed before a definite conclusion can be drawn. The specificity of the effects is not yet clear, particularly since most tested substances affect ICSS per se. Moreover, other studies dealing with the interaction between the effects of naloxone and cocaine or haloperidol on the threshold for ICSS suggested the existence of separate dopaminergic and opioid mechanisms modulating ICSS (Van Wolfswinkel et al., 1988).

A pivotal role for dopaminergic mechanisms, especially the mesocorticolimbic pathway, in opioid-induced place-conditioning has been proposed. The suggested involvement of mesocorticolimbic DA in opioid-place preference stems from the observations that infusion of opioids into the VTA, but not the substantia nigra, induced place preference (Phillips and LePiane, 1980, 1982; Phillips et al., 1983; Bozarth, 1987b; Bals-Kubik et al., 1993). The conditioned place preference induced by intra-VTA administration of [D-Ala²]-Met-enkephalin could be blocked by systemic administration of the DA antagonist haloperidol, as well as lesioning the mesocorticolimbic pathway, by infusing 6-OHDA into the ipsilateral median forebrain bundle (Phillips et al., 1983). Systemic treatment with DA antagonists blocked the development of opioid-induced place preference although in some studies, no such effect was found (Bozarth and Wise, 1981a; Spyraki et al., 1983; Mackey and Van der Kooy, 1985; Leone and Di Chiara, 1987; Hand et al., 1989; Kivastik et al., 1996). The DA antag-

onist α-flupenthixol blocked the aquisition of heroin-induced place preference when a dose of 0.5 mg/kg, but not when a dose of 0.05 mg/kg heroin, was used as unconditioned stimulus (Nader et al., 1994). In addition, chronic treatment with flupenthixol before conditioning enhanced the acquisition of heroin-induced place preference, and *d*-amphetamine enhanced the place preference induced by low doses of morphine (Stinus et al., 1989; Gaiardi et al., 1998). Dopaminergic lesions of the NAC inhibited the acquisition of place preference induced by heroin or morphine and the place aversion induced by U69,593 (Spyraki et al., 1983; Shippenberg et al., 1993). In addition, the aversive effects of intra-VTA-administered CTOP, but not intra-NAC administered naloxone, were inhibited in rats with 6-OHDA lesions of the NAC (Shippenberg and Bals-Kubik, 1995). The involvement of DA in opioid-induced place-conditioning was suggested to be mediated, especially through DA D1 receptors. That is, treatment with the DA D1 antagonist SCH23390 attenuated the development of place preference induced by morphine, as well as the δ receptor agonists BW373U86 and SNC-80, and the place aversion induced by naloxone and U69,593 (Leone and Di Chiara, 1987; Shippenberg and Herz, 1987, 1988; Acquas et al., 1989; Longoni et al., 1998). Infusion of SCH23390 into the NAC mimicked its effects on opioid place-conditioning after systemic administration, suggesting the NAC as a possible site of action (Shippenberg et al., 1993). Systemic, as well as intra-NAC treatment with DA D2 antagonists such as spiperone and sulpiride, did not affect opioid-induced place-conditioning (Shippenberg and Herz, 1988; Shippenberg et al., 1993). However, in view of the findings that systemic treatment with haloperidol and pimozide, which display selectivity for DA D2 over DA D1 receptors, did inhibit morphine- and heroin-induced place-conditioning, an involvement of DA D2 receptors in opioid-induced place-conditioning seems likely as well (Bozarth and Wise, 1981a; Spyraki et al., 1983; Leone and Di Chiara, 1987; Hand et al., 1989). In addition, the DA D2/D3 agonist 7-hydroxy-dipropylaminotetralin, which in a variety of studies has been shown to act as a functional DA-antagonist, inhibited both the acquisition and expression of morphine-induced place preference (Rodriguez De Fonseca et al., 1995). Moreover, in knockout mice lacking DA D2 receptors, conditioned place preference could not be established with morphine (Maldonado et al., 1997). Taken together, these results support the hypothesis that opioid-induced place preference, as well as κ agonist- and μ antagonist-induced conditioned place aversion are mediated through the mesocorticolimbic DA system. With respect to δ agonist-induced place preference, it has been reported that in mice the place preference induced by i.c.v. DPDPE (δ_1-selective) but not by i.c.v. [D-Ala²]-deltorphin (δ2-selective) was antagonized by the DA D1 antagonist SCH23390 and not by sulpiride (Suzuki et al., 1996c).

In conclusion, although there seems some evidence of a role of brain DA in opioid dependence, as revealed from animal experiments, the precise role is not yet elucidated. Studies using the self-administration paradigm, measuring the positive reinforcing effects of opioids among others, do not suggest a critical role for NAC DA for opioid reinforcement. The limited studies on the interaction between DA and opioids in the ICSS procedure do not allow definitive conclusion to be drawn. Data from conditioned place preference studies reveal a critical role of NAC DA receptors in conditioned place preference and aversion induced by opioid agonists and antagonists. The place preference method involves classical conditioning rather than operant conditioning as involved in self-administration and ICSS. In addition, although self-administration and ICCS provide measures of reinforcement, data gathered using place preference are hard to interpret but most likely represent some motivational effects of the drugs used. Thus, DA mechanisms may be more involved in the distinct conditioning and certain motivational processes concerned in opioid dependence than in opioid reinforcement (Robinson and Berridge, 1993; Wolterink et al., 1993; Kiyatkin, 1995; Robbins and Everitt, 1996; Salamone, 1996; Nader et al., 1997; Schultz et al., 1997). Accordingly, the unconditioned reinforcing properties of food and sexual stimuli appeared to be intact after accumbens DA depletion and the functions of accumbens DA may be related to the behavioral responsiveness to conditioned stimuli and to the organization of goal-directed behaviors (Kiyatkin, 1995; Salamone, 1996; Nader et al., 1997). In conclusion, more studies are needed to elucidate the significance of brain DA systems in the dynamics of opioid dependence, in particular since neuroleptics are not the drugs of choice to treat human opioid addicts (Practice Guideline American Psychiatric Association, 1995).

VIII. Addiction and Endogenous Opioids

In this section the role of brain opioids in dependence on opiates and on other drugs will be discussed. In clinical practice the term opiate addiction is normally used, and especially heroin, morphine, and opium are consumed by addicts. In trying to discuss the significance of the experimental data and psychological concepts as described before for drug dependence (see *I. Addiction*), it is worthwhile to delineate four stages in the addiction course: the initiation phase, maintenance phase, withdrawal phase, and relapse phase. Different psychological and biological mechanisms seem to be important for the drug use in these stages.

The first contact between an individual and an opiate is usually in the context of a medicinal treatment of an illness, e.g., severe pain, or by the desire to experience the effect of the drug. As mentioned before, medicinal treatment with opiates will evoke the addiction habit in a very small percentage of the individuals only and is not an issue of major concern. The desire to experience the effect of the drug is usually stimulated by the environment of the individual, either because the person is informed about the marvelous effects or in his or her setting the drug is used. Whether or not the opiate use will be continued depends among others on the subjective effects of the drug—whether the drug is liked—and/or the expectation that this positive subjective effect will be (re-)experienced on repeated use. The positive subjective effects may include euphoria (feeling of well being) and even ecstasy, which exceed the possible negative effects. The subjective experience with the first use of the drug may also be influenced by whether or not the person has used other drugs before or is addicted to other drugs. In particular, addicts are quite sensitive to the subjective effects of drugs and can discriminate well between the effects of various drugs. Regular use can result in psychic dependence, characterized by more or less compulsive drug use.

It is quite obvious that not all individuals who experienced the drug and even regularly used the drug will reach the stage of psychic dependence. In fact, a vast majority of people that at some time experiences the drug will not develop an addiction. Thus, the question emerges why some individuals are more susceptible to develop psychic dependence than others. Although social factors and context may be important in this respect, the drug-induced neuroadaptation underlying psychic dependence may play an important role in the individual susceptibility to develop psychic dependence. During the initiation phase of opiate addiction, the positive reinforcing effects of the drug and the vulnerability of the individual for the development of the dependence are important issues. The positive subjective effects like euphoria have been linked to the reinforcing or rewarding effect of the drug and may be important why the drug is liked, although convincing evidence for this statement is not available. Whether physical dependence may already play a role in the initiation phase of opiate addiction is not known. Experimental animal data however indicate that physical dependence hardly contributes to the development of opioid self-administration (Woods and Schuster, 1971; Van Ree et al., 1978; Dai et al., 1989). The process of initiation of addiction to other than opiate drugs is quite similar as described for opiates, but the duration of this phase varies among drugs (e.g., compare heroin and alcohol).

Opioids are reinforcing and enhance ICSS. These actions are mediated by μ receptors, at least for an important part (see *III. Self-Administration* and *IV. Intracranial Electrical Self-Stimulation*). The brain site of the reinforcing action of opioids is still a matter of debate, although the VTA is a sensitive site in this respect. The suggestion however that the mesolimbic dopaminergic system, in particular the ventral tegmental-accumbal pathway, is the site of action, has not been substantiated by experimental data. It is also not clear whether one particular site or various sites within one circuit or

different brain circuits are involved in the primary reinforcing action of opioids, leaving space for the concept of multiple brain reinforcement systems that can be activated by opioids.

Endogenous opioids exert, like opiates, a reinforcing action and are self-administered by experimental animals. This has led to the postulate that the reinforcing actions of nonopioid drugs might be mediated by endogenous opioids. This, however, is not supported by the experimental data. For example, cocaine reinforcement in rats is not blocked by opioid antagonists (e.g., De Vry et al., 1989a). However, a modulatory role of endogenous opioids in cocaine reinforcement seems likely, as evidenced among others by the observation that the dose-response curve for cocaine reward during initiation of self-administration was shifted to the right by the opioid antagonist naltrexone. Thus, endogenous opioids may be implicated in the susceptibility of individuals for the reinforcing effects of drugs. Accordingly, opioid antagonists attenuated, but did not block the ICSS and long-term treatment with opioid antagonists can alter the setpoint for ICSS (see *IV. Intracranial Electrical Self-Stimulation*). The modulation of drug reinforcement by endogenous opioids may be mediated by μ receptors, but other opioid receptors may also contribute, e.g., the κ agonist U50,488H decreased the intake of cocaine and morphine when offered in doses that initiate self-administration behavior and induced self-administration behavior with lower, subthreshold doses of cocaine and morphine (Kuzmin et al., 1997b). Little is known about the brain site of this modulatory role of endogenous opioids in drug reinforcement, but the VTA seems a candidate is this respect as evidenced by the effects of opioid antagonists injected into this area. Whether the ventral tegmental-accumbal dopaminergic system is involved as well is unknown. The modulatory role of endogenous opioids may be pertinent to the transition of drug experience to regular use and to compulsive use in a certain individual. It may be postulated that a low endogenous opioid activity in the brain makes the individual less vulnerable to develop (psychic) dependence (see data about endogenous opioids and sensitivity to ethanol, *VI. Endogenous Opioids and Nonopioid Drugs of Abuse*). Factors that contribute to this vulnerability, like the genetic makeup and environmental factors e.g., contact with drugs during development and stress, may exert their effects at least partly via the endogenous opioid systems.

The transition of the initiation phase to the maintenance phase of the addiction course is not well defined. During maintenance, compulsive drug use is present, indicating that psychic dependence has developed. The drug is not only liked but also wanted. Conceptually, these feelings are quite different and are likely to be mediated by different mechanisms (Robinson and Berridge, 1993; Nader et al., 1997). Several distinct brain processes may generate wanting the drug. There are the unconditioned effects of the drug: the positive reinforcing action, which may be important for liking the drug—although liking may become less important when the addictive habit continues—and the acute withdrawal reactions and feelings (negative reinforcement), particularly in case of opiate and alcohol addiction. It should, however, be kept in mind that both in animals and humans the significance of the typical withdrawal syndrome in opiate or alcohol addiction is probably overestimated. Besides, conditioned effects of the drug can contribute to the addictive habit (Wikler, 1973). Both the positive and the negative action can be conditioned: conditioned incentives, which may result in the phenomenon of the "needle freak" and conditioned withdrawal (O'Brien et al., 1974, 1977). In addition, craving has been or is developed during the maintenance phase. Craving will be discussed later, when describing relapse.

These unconditioned and conditioned effects have been described for opiates in humans but also in experimental animals. The brain sites involved in opioid withdrawal can be separated from those involved in opioid reinforcement (Bozarth and Wise, 1984). The process of conditioning to the positive and aversive effects of opioids may take place in other distinct brain systems, e.g., in the amygdala-hippocampus-accumbal complex and may not be different from the process of conditioning in general (Robbins and Everitt, 1996). Accordingly, in place preference studies wherein unconditioned positive effects of the drug are conditioned have indicated that the ventral tegmental-accumbens dopaminergic system is of importance. It should however be mentioned that it is yet unknown which particular effect of the drug is conditioned in the place preference procedure. The NAC is also a sensitive site for place aversion induced by opioid antagonists in animals physically dependent on morphine (Schulteis and Koob, 1996). This nucleus along with its input systems may be important for the salience attribution to neutral stimuli, which process may be relevant for wanting the drug (Robinson and Berridge, 1993; Nader et al., 1997).

The role of endogenous opioids during the maintenance phase of addiction is not clear. It may be that the endogenous opioids are involved in conditioning of positive and aversive effects of opiates and other drugs. Using the place preference procedure, it has been shown that μ ligands induce place preference and κ ligands induce place aversion. This could be elicited by modulating the ventral tegmental-accumbal dopaminergic system. Accordingly, opioid antagonists probably via blocking μ-opioid receptors attenuate the acquisition and expression of cocaine-induced place preference. Some evidence is available that endogenous opioids may play a role in the dynamics of daily drug intake. Just before a scheduled next session of daily drug intake, the levels of β-endorphin in the anterior part of the limbic system were decreased in animals self-injecting heroin or cocaine (Sweep et al., 1989). In addition, at that time

indications for release of endogenous opioids in some limbic brain areas have been found in animals self-injecting cocaine or ethanol (Gerrits et al., 1999). These effects have been linked to the desire and/or the need for the drug probably present at that moment and may thus be related to craving and/or dysphoria present in a human addict before drug-taking. Since at the same time the basal release of DA in the NAC is decreased (M. A. F. M. Gerrits, P. Petromilli, H. G. M. Westenberg, G. Di Chiara, J. M. Van Ree, unpublished data), the endogenous opioids and mesolimbic DA, separately or interactively, may be implicated in subjective feelings of addicts leading to daily drug intake.

The third stage of the addiction course is the withdrawal phase. Heroin and alcohol addicts frequently experience withdrawal, either or not with medicinal and psychological support. The contribution of this experience and of the conditioning of withdrawal symptoms to the addictive behavior is not well understood. As in humans, both somatic and affective symptoms of withdrawal can be observed in animals (Schulteis and Koob, 1996). Somatic symptoms include among others, weight loss, diarrhea, wet dog shakes, jumping, penile erection, ptosis and teeth chattering, and affective symptoms elevation of ICSS threshold, suppression of operant responding, reduced exploration, and place aversion. Different brain sites have been implicated in these sets of symptoms, i.e., the periaquaductal gray in the somatic symptoms and the NAC in the affective symptoms. Data from experimental animals indicate that endogenous opioids can induce physical dependence and the related occurrence of typical withdrawal symptoms upon discontinuation. The significance of endogenous opioids in the withdrawal phase has yet to be elucidated. Maybe alterations in the endogenous opioid systems during this phase have influences on the next stage, relapse. Rhesus monkeys who had about 1 year of experience with free-choice alcohol-drinking appear to be more sensitive for naltrexone, with respect to the naltrexone-induced decrease of alcohol consumption, after a period of imposed abstinence as compared to the condition of continuous access to alcohol, indicating changes in the endogenous opioid systems during a period of abstinence (Kornet et al., 1991).

The fourth phase of the addiction course, the relapse phase, is quite important from a theoretical and a therapeutic viewpoint of addiction (O'Brien, 1997). The major problem of treating addicts is not discontinuation of drug taking, but the relapse in their former addiction habit sooner or later after discontinuation of drug-taking. In experimental animals, it has been shown that after extinction of self-administration behavior, priming with the drug used or another drug of abuse induces responding on the lever associated with receiving the drug (Stewart et al., 1984). Similar responding could be induced by experimental stress. This indicates that conditioned drug effects but also other events like stressful experiences are important for reinitiating drug self-administration. In the period(s) of drug-taking and abstinence, brain mechanisms are changed, probably leading to homeostatic dysregulations, in which processes like sensitization and counteradaptation may be involved (Koob and Le Moal, 1997). These changes may contribute to the vulnerability to relapse in individuals with a history of addiction.

An important issue in relapse is craving. Craving, the intense desire to use the drug , is already present during the maintenance phase but also long after discontinuation of drug-taking. Whether the craving during maintenance and after discontinuation is mediated by the same brain mechanisms is not known but likely. Craving develops during repeated drug use and has been theoretically explained by the process of incentive sensitization (Robinson and Berridge, 1993). The addicts may, by taking the drug, become sensitized to the drug and the drug-associated stimuli and therefore want the drug more and more, which could lead to compulsive drug-seeking and drug-taking. This process is suggested to result from incremental neuroadaptations. It has been argued that the ventral tegmental-accumbal dopaminergic system may play a role in this respect, although other systems present in the limbic area have been implicated as well. Indeed, chronic opioid exposure induces long-lasting molecular and cellular adaptations among others in the VTA and the NAC, in which transcription factors, glutamatergic transmission, neurotrophic factors, and neurofilament proteins may be involved (Kalivas and Stewart, 1991; Self and Nestler, 1995; Spanagel, 1995). The neuroadaptation remains long after drug discontinuation and perhaps more or less during the entire life of the individual. The relationship between craving present long after discontinuation of drug-taking and the affective effects conditioned during drug-taking and abstinence and the (conditioned) expectations induced during these periods is not clear. Several animal models have been proposed to investigate drug-craving (Markou et al., 1993), but have hardly been used to investigate the significance of endogenous opioids in drug-craving. Endogenous opioids may play a role in the expression of conditioned place preference with addictive drugs, that may measure aspects of drug-craving (see *VI. Endogenous Opioids and Nonopioid Drugs of Abuse*).

The administration of opioids and other drugs of abuse can be accompanied by the development of tolerance and sensitization to the effects of the drug. The actual intake of drugs in human addicts and self-administering animals is quite stable for months and years, suggesting that tolerance nor sensitization to the drugs' reinforcing action is hardly present. It may, however, be that both tolerance to certain nonreinforcing and aversive effects of the drug and sensitization to some motivational effects may contribute to the vulnerability of the individual to become dependent. Moreover,

as already outlined, neuroadaptations underlying drug sensitization may also be implicated in craving and in the vulnerability to relapse.

In conclusion, endogenous opioids seem to be involved in addictive behavior. Although their significance is not yet established, there are indications for a modulatory role in drug reinforcement, which may be pertinent for the individual susceptibility with respect to development of (psychic) dependence, for a role in the dynamics of drug-taking behavior during the maintenance phase of drug dependence and for a role in certain motivational effects induced by repeated drug (self-)administration, which may be involved in craving and relapse. Different brain opioid systems have been concerned in addictive behavior: opioid systems in the VTA have been implicated in the modulatory role of endogenous opioids in drug reinforcement, whereas opioid systems in limbic areas may be involved in the dynamics of drug-taking behavior and in craving and relapse.

In addition, various opioid receptors may be involved, evidenced among others by the dose of opioid antagonists needed to antagonize certain effects. Low doses of these drugs affect heroin intake of animals during i.v. heroin self-administration, alcohol intake of monkeys, particularly after a period of abstinence, and cocaine-induced place preference (e.g., Koob et al., 1984; Kornet et al., 1991; Gerrits et al., 1995). For some other effects, higher doses of these drugs are needed. μ-Opioid receptors seem to be the main opioid receptor involved in different aspects of addictive behavior. Concerning the role of other opioid receptors, i.e., δ and κ, more experimentation is needed before a definitive conclusion can be made about their role in addictive behavior, although a role of κ-opioid receptors has been proposed in some processes of sensitization. It is obvious that motivational processes either or not activated or induced by drugs of abuse play important roles in drug dependence and the addiction course. It should however be emphasized that the concerned motivational processes vary and are quite different during the various stages of the addiction course. The involvement of multiple motivational processes along with, among others, multiple brain reinforcement systems and the pharmacological heterogeniety of drugs of abuse contribute to the complexity of drug dependence and make it very unlikely that a particular brain site or system can be assigned as the most important for drug dependence. This conclusion should be kept in mind when treating human addicts. In addition, it should be stressed that drug dependence is a psychiatric, chronic relapsing disease and not simple a matter of using drugs (Leshner, 1997).

IX. Perspectives

Opium, morphine, and related drugs were fascinating substances for the ancient Greeks but also are for the generation of the 21st century. These substances can control pain quite well in many patients, but can also evoke addiction. To analyze the mechanisms involved in opioid addiction, many investigations have been performed for decades. Historically, highlights were the demonstration of i.v. opioid self-administration in experimental animals, the finding of ICSS, and the discovery of endogenous opioids in the brain. Evidence emerged that the brain contains substances that can elicit addiction and the machinery for the process of dependence. This has markedly changed the concepts of addiction.

From a clinical point of view, important issues in substance dependence are the vulnerability of the individual for the dependence-creating properties of the substance and the relapse of addicts into their former habit of drug-taking behavior. Animal experimentation can contribute to the understanding of these phenomena and may delineate factors that could be used in clinical practice. For example, the effects of opioid antagonists on alcohol consumption in animals has ultimately lead to the introduction of naltrexone for treatment of relapse in alcoholics. Detailed animal research on the mentioned issues, i.e., vulnerability and relapse, has only recently been initiated. Models for craving, probably an important aspect in the phenomenon of relapse, are being developed. Biochemical research can unravel the mechanisms underlying the process of neuroadaptation involved in development of dependence and craving.

From the present review, it can be concluded that endogenous opioids probably play a role in the vulnerability to become dependent, the daily dynamics of drug-taking, and the relapse. However, different endogenous opioids systems may be involved, present in the VTA and the limbic system, respectively. It seems that the encounter among biology, psychology, and medicine was fruitful and that stimulation of multidisciplinary research can contribute to further understanding of the intriguing phenomenon of addiction. Macht (1915) concluded his review in the beginning of this century with, "If we trace the history of opium from its earliest beginnings to the brilliant researches of recent years, if we but compare the analytic and synthetic, chemical, physiologic and pharmacological studies of the same old drug with the fantastic and puerile effusions on the subject of our medical predecessors, we cannot help being impressed with the long strides forward which medicine has made; yet, on the other hand, our very recent studies on opium and its alkaloids serve but to emphasize the more our meager knowledge of the subject and the still greater task before us".

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