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Diversity of Agents That Modify Opioid Tolerance, Physical Dependence, Abstinence Syndrome, and Self-Administrative Behavior*

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I. Introduction

Opioid drugs are widely used for the treatment of pain of moderate to severe intensity, such as the pain in carcinoma, in biliary or renal colic, and after surgery. Opioids relieve painful stimuli by interacting with three major types of receptors, namely, μ, δ, and κ, in various brain regions and spinal cord. The typical agonists for these receptors are morphine or D-Ala^2,MePhe^4,Gly-ol^5 enkephalin (μ-), ethylketocyclazocine or U-50,488H (κ-), and D-Pen^2,D-Pen^5 enkephalin (δ-) (Bhargava, 1991a). Once the existence of opioid receptors in mammalian brain was established, the search for the endogenous ligand for the receptors resulted in the identification and isolation of three major types of opioid peptides, namely, enkephalins, dynorphins, and β-endorphin. They are derived from three distinct genetic precursors, namely, preproenkephalin, prodynorphin, and proopiomelanocortin, respectively. The endogenous opioids exhibit differential activity at the three opioid receptors. The enkephalins and dynorphins exhibit affinity predominantly for δ- and κ-receptors respectively, whereas β-endorphin has mixed action on μ- and δ-receptors. In addition, a separate receptor, ε, has been suggested to exist for β-endorphin in mouse vas deferens.

Although both exogenous and endogenous opioids produce pain relief, chronic administration of these drugs for a long time and, particularly, at high doses results in the development of tolerance to their analgesic and other pharmacological actions. The development of physical dependence on these drugs, however, depends on the nature of the drug. In general, drugs acting on μ-opioid receptors produce a high degree of physical dependence, as evidenced by the appearance of severe distressing physical symptoms called the abstinence syndrome. Some, but not all, of these symptoms are relieved by readministering the same drug or a similar type of drug. These drugs, such as morphine or heroin, are considered to be highly addictive. κ-Opioid drugs either do not

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produce physical dependence or produce a very mild degree of dependence and are generally labeled nonaddicting drugs. δ-Opioids which are all peptides in nature generally do not produce physical dependence. However, drugs such as β-endorphin, when administered chronically into the CNS,‡ can produce addictive behavior (Wei and Loh, 1976). Addiction processes generally constitute tolerance, physical dependence, abstinence syndrome, and self-administrative behavior. The biochemical or molecular mechanisms involved in these four processes are still the subject of intense investigation. A wide variety of agents have been reported to modify the opioid addiction processes not only in animals but also in humans.

The Medication Development Division of the National Institute on Drug Abuse and others (Drs. R. S. Rapaka and H. Sorer, personal communication) are intensely searching for nonaddicting opioids and/or agents that can prevent or reverse the addiction processes. Thus, drugs are being explored that can be used prophylactically in conjunction with opioids to block tolerance and physical dependence or, when given to opioid-dependent subjects, can restore the therapeutic benefits and eliminate the adverse effects of opioids.

Additionally, the new therapeutic agents are also explored for their ability to inhibit opioid-induced abstinence syndrome and self-administrative behavior. The purpose of this review is to identify these agents, classify them in various categories based on their chemical characteristics or specific receptor selectivity, analyze their actions as reported by different investigators, and identify consistencies or inconsistencies in their actions. Some of these agents have been used based on identified mechanisms, and the others have no rationale, indicating that the opioid addiction processes may possibly involve multiple molecular mechanisms operating at different sites in the body. In some cases drugs that modify opioid addiction processes have been discovered serendipitously. Even if the mechanism of action of a particular agent in modifying chronic actions of opioid is not known, it can eventually lead to the development of potentially beneficial therapeutic agents to manage opioid addiction processes. Before the effects of various drugs on the addictive processes are described, a brief description of the animal models used for developing tolerance, physical dependence, and self-administration will be provided. Major emphasis will be given to morphine which produces tolerance, physical dependence, abstinence syndrome, and self-administrative behavior. However, studies with κ-opioid receptor agonists which produce tolerance to their pharmacological actions, particularly to their analgesic and hypothermic effects, but mild physical dependence, will also be described. A comparison of the effects of drugs on μ- and κ-opioid receptor agonist-induced tolerance can then lead to the understanding of the mechanisms involved in such processes. Finally, chemical structures of some agents that may show promise in the treatment of opioid addiction are also given. They may lead to the synthesis and biological evaluation of newer analogs.

‡ Abbreviations: CNS, central nervous system; i.p., intraperitoneal; s.c., subcutaneous; i.v., intravenous; i.c.v., intracerebroventricular; i.t., intrathecal; TRH, thyrotropin-releasing hormone; i.m., intramuscular; MIF, melanocyte-stimulating hormone release-inhibiting factor; CCK, cholecystokinin; FMRF-NH_2, Phe-Met-Arg-Phe-NH_2; NPFF, neuropeptide FF; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine, serotonin; cAMP, cyclic 3′,5′-adenosine monophosphate; PIA, (−)-N^6-(*R*-phenylisopropyl)-adenosine; NMDA, N-methyl-D-aspartate; PCP, phencyclidine; NMMA, N^G-monomethyl-L-arginine; NOS, nitric oxide synthase; Δ^9-THC, *l-trans*-Δ^9-tetrahydrocannabinol.

II. General Procedures to Develop Opioid Tolerance, Physical Dependence, Abstinence Syndrome, and Self-Administrative Behavior

A. Morphine, a μ-Opioid Receptor Agonist, Induced Tolerance and Physical Dependence

Experimental animals and humans have been utilized to determine the effects of drugs on the opioid addiction processes. The animals include mice, rats, guinea pigs, and monkeys. Morphine produces a plethora of pharmacological actions. Chronic administration of morphine produces tolerance to its analgesic, hypothermic, hyperthermic, respiratory depressant, euphoric, cataleptic, locomotor depressant, and stimulant actions. A majority of the studies have been concentrated on the tolerance to the analgesic action of morphine. The analgesic tolerance has been generally measured by using the tail-flick test, hot plate test, or the acetic acid-induced writhing test. Chronic administration of morphine also results in the development of physical dependence as evidenced by the appearance of distressing physical symptoms following its withdrawal. These symptoms and their intensity vary with the degree of dependence and the species used. In a majority of the studies, rodents have been used. For further confirmation of the results, guinea pigs or monkeys have been utilized. Earlier studies had utilized multiple i.p. or s.c. injections of morphine in increasing doses to develop dependence in the rat (Bhargava and Matwyshyn, 1977; Domino and Wilson, 1973; Maynert and Klingman, 1962). This method requires a long period for the animal to become addicted. Administration of morphine by the i.v. route has been used for inducing morphine addiction in rats (Kumar et al., 1968; Numan et al., 1975; Schuster and Thompson, 1969; Weeks, 1962). Morphine tolerance and dependence have also been induced in the rat by administering the drug in drinking water, saline, or sucrose solution (Badawy et al., 1982; Khavari and Risner, 1973a,b). The most rapid and convenient method for inducing morphine tolerance and physical dependence in rodents has been the s.c. implantation of specifically formulated pellets of morphine free base (Bhargava, 1977b, 1978a; Blasig et al., 1973; Maggiolo and Huidobro, 1961; Way et al., 1969; Wei et al., 1973). Although the pellet implantation pro-

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cedure offers convenience, it suffers from the disadvantage that there is a rapid release, followed by slow, sustained release of morphine from the pellet. This situation may be slightly different from that observed in humans.

Two other methods have also been used. They include injection of a large dose (100 mg/kg) of morphine in mice to induce a state of acute tolerance 4 h later (Abdelhamid et al., 1991) and the implantation of osmotic minipumps containing morphine solution, which can be delivered at a predetermined rate (Werling et al., 1989). The minipumps can also be used to deliver the morphine s.c. or directly into the brain.

B. Morphine Abstinence Syndrome

As indicated earlier, the symptoms of withdrawal can be induced either by abrupt termination of morphine treatment or by injecting an opioid receptor antagonist, such as naloxone, nalorphine, naltrexone, or levallorphan (Bhargava, 1978a; Koyuncuoglu et al., 1979). The symptoms of abrupt and antagonist-induced withdrawal differ in their quality, onset, intensity, and duration (Bhargava, 1977a; Blasig et al., 1973). In morphine-dependent subjects, the nature of the symptoms depends on the species studied. Some of the withdrawal symptoms for mice, rats, monkeys, and humans are provided in table 1. In the majority of the studies in mice, naloxone- or naltrexone-induced stereotyped jumping behavior (a hyperactivity response) and changes in the body weight and body temperature have been monitored. In rats, several other symptoms such as teeth chattering, wet-dog shakes, ptosis, penile erection, and lacrimation have also been monitored in addition to jumping or escape behavior and changes in the body weight and body temperature (Bhargava, 1977b; Blasig et al., 1973; Wei et al., 1973). It has been observed that particular drugs modify only some, but not all, symptoms of the abstinence syndrome.

C. Morphine Self-Administrative Behavior/Volitional Consumption

Self-administrative behavior of the addicting opioids, particularly morphine, has been studied in rats and monkeys. Administration of morphine by the i.v. route has been used in rats (Weeks and Collins, 1979) and monkeys (Deneau et al., 1969). Others have utilized i.c.v. injections of morphine (Dib and Duclaux, 1982) and presentation of food admixed with morphine (oral) for self-administration studies (Yanaura et al., 1980; Yanaura and Suzuki, 1978).

D. κ-Opioid Receptor Agonist-induced Tolerance and Physical Dependence

A number of compounds exist that interact with κ-opioid receptors with different selectivity. They include compounds such as pentazocine and butorphanol which are in clinical use and others such as bremazocine, cyclazocine, ethylketocyclazocine,and ketazocine (Lahti et al., 1985). The benzomorphan κ-opioid receptor agonists (fig. 1) do not substitute for morphine in the dependent monkey (Swain and Seevers, 1974, 1976; Villareal and Seevers, 1972), and therefore, selective κ-opioid drugs are being discovered to be used as potential analgesic agents. Von Voigtlander et al. (1983) reported the pharmacological profile of a highly selective κ-opioid receptor agonist that did not have the benzomorphan nucleus. This compound, *trans*-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide (U-50,488H), and its analog, (5α,7α,8β)-(+)N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro (4,5)dec-8-yl)]benzeneacetamide (U-69,593) (fig. 2), display analgesic action in a variety of tests in mice and rats, produces tolerance when administered chronically but does not produce morphine-type physical

TABLE 1

Some of the commonly observed signs/symptoms of abstinence syndrome in morphine-dependent subjects

Mice	Rats	Monkeys	Humans
Hyperactivity	Hyperactivity	Lying on side	Craving, anxiety, tears, and runny nose
Stereotyped jumping	Stereotyped jumping	Drowsiness	Sweating, yawning, and difficulty in sleep
Weight loss	Weight loss	Fighting	Mydriasis, piloerection, and tremors
Hypothermia	Hypothermia	Avoiding contact	Hot and cold flashes
Urination	Urination	Vocalization	Aching bones and muscles and anorexia
Defecation	Defecation/diarrhea	Crawling and rolling	Insomnia, restlessness, and nausea
	Lacrimation	Restlessness (pacing)	Increased blood pressure and hyperthermia
	Teeth chattering	Ptosis	Increased respiratory rate and pulse rate
	Penile erection	Tremors	Curled-up position, vomiting, and diarrhea
	Ptosis	Retching	Weight loss
	Wet-dog shakes	Vomiting	Spontaneous ejaculation or orgasm
	Salivation	Coughing	
	Writhing	Salivation	
	Elevated blood pressure		
	Grooming		
	Rearing		
	Scratching		
	Aggression		

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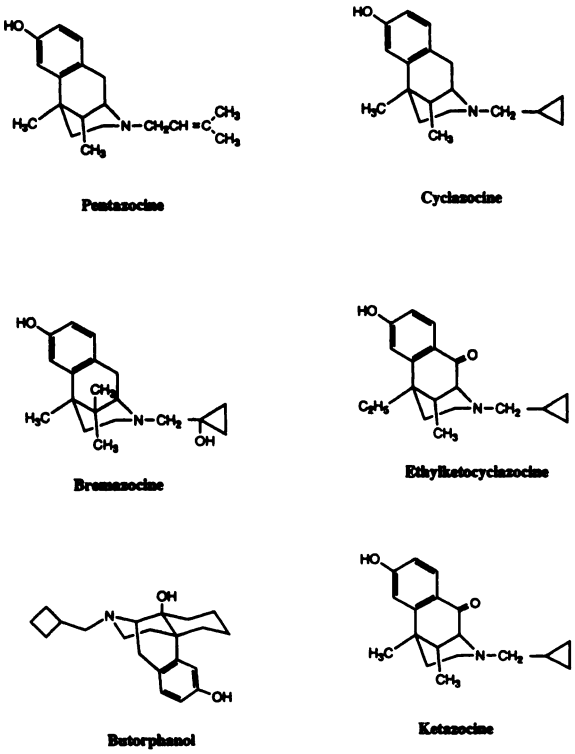

FIG. 1. Structures of mixed agonist-antagonist opioids.

dependence, inhibits the binding of [^{3}H]ethylketocyclazocine, and causes sedation, diuresis, and corticosteroid elevation. Spiradoline (U-62,066) (fig. 2), an analog of U-50,488H, has been synthesized but was found to be less selective for κ-opioid receptors (Von Voigtlander and Lewis, 1988). In a majority of the studies dealing with κ-opioid receptor agonist-induced tolerance, U-50,488H has been utilized in mice and rats. Mice have been rendered tolerant to U-50,488H by two or three daily s.c. injections of increasing doses of the drug for 2 to 3 days (Von Voigtlander et al., 1983). In our laboratory, tolerance to U-50,488H has been induced in mice and rats by twice daily i.p. injections of the drug (25 mg/kg) for 4 days, and the testing has been done on day 5. A high degree of tolerance to the analgesic and hypothermic actions of U-50,488H develops as a result of this procedure (Bhargava et al., 1989a,b, 1991c, 1994; Bhargava and Thorat, 1994; Gulati et al., 1989; Thorat et al., 1993; Veeranna et al., 1992, 1993).

E. Mixed Opioid Agonist-Antagonist Analgesic-induced Tolerance and Physical Dependence

Butorphanol (Stadol) is a mixed opioid agonist-antagonist analgesic that is used primarily as a parenteral drug. It produces its action by interacting with all three types of opioid receptors. Physical dependence on butorphanol in humans is evidenced by the appearance of withdrawal symptoms such as rhinorrhea, gastric distress, vomiting, dysphoria, emotional lability, and irritability (Brown, 1985). Butorphanol dependence has been produced in the rat by continuous i.c.v. infusion (26 nmol/h) for 3 days utilizing osmotic minipumps (Alzet 2001). Withdrawal symptoms appear in rats treated chronically with butorphanol following i.c.v. injection of either δ- or κ-opioid receptor antagonists (Jaw et al., 1993a,b). Buprenorphine (Temgesic) is another drug that also has mixed opioid agonist-antagonist activity. Tolerance to the analgesic and hyperthermic effects of buprenorphine has been induced in the rat by s.c. injections of the drug (0.5 mg/kg) twice a day for 4 days (Bhargava, 1982b).

The goals of developing an ideal pharmacotherapeutic agent to prevent the development of tolerance to and physical dependence on opioids are that it should (*a*) not antagonize the analgesic activity of the opioid, (*b*) selectively block tolerance to the analgesic action but not to the respiratory depressant action, (*c*) block the physical dependence symptoms, i.e., peripheral and CNS-mediated behaviors, (*d*) be orally effective with a long biological half-life, (*e*) have minimal side effects, and (*f*) have no long-term toxicity or adverse effects.

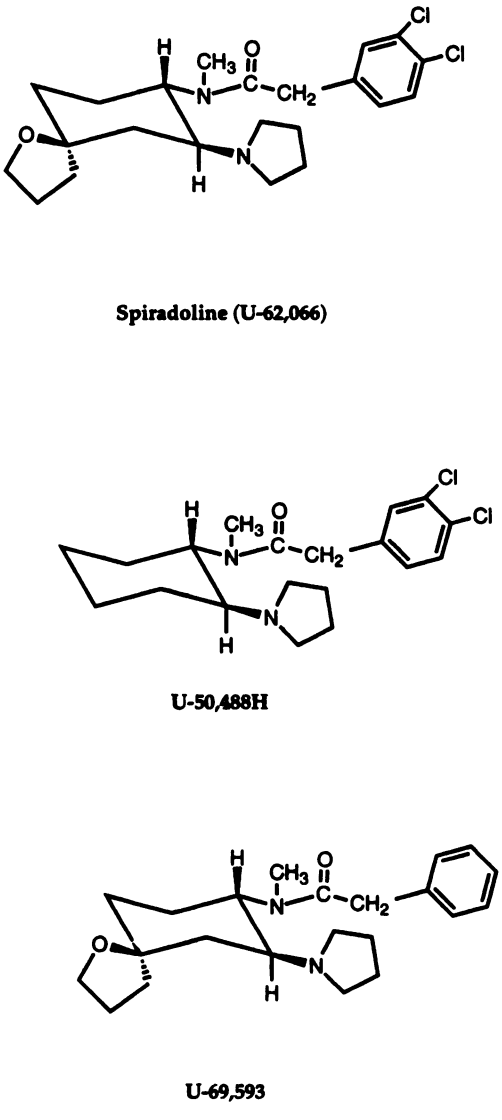

FIG. 2. Structures of selective κ-opioid agonists.

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Drugs from several different chemical and pharmacological classes have been shown to modify opioid tolerance, physical dependence, symptoms of abrupt and/or antagonist-induced abstinence syndrome, and self-administrative behavior. These agents are synthetic, semisynthetic, or derived from natural products. Some of them have more or less known mechanisms of action, whereas others were found serendipitously to have action on opioid addiction processes.

In the following sections, the effects of various drugs known to modify the chronic actions of morphine, U-50,488H, and mixed opioid agonist-antagonist analgesics in animals will be described. Additionally, wherever it is possible, the chemical structures and their mechanism of action will be provided. Finally, for each class of drug used, the basic mechanism involved in the opioid addiction processes that led to the use of a specific agent to modify these processes will be described briefly.

III. Drugs That Modify Opioid Tolerance and Physical Dependence Processes

A. Drugs Related to Opioids

1. Opioid receptor agonists and antagonists. a. UNIVERSAL OR NONSPECIFIC OPIOID RECEPTOR ANTAGONISTS. Opioid antagonists such as nalorphine, nalmefene, naloxone, and naltrexone (fig. 3a), which antagonize the responses mediated by μ-, δ-, and κ-agonists, modify tolerance/dependence on morphine. Although the changes in brain and spinal cord μ-, δ-, and κ-opioid receptors in morphine tolerance and abstinence are not consistent (Abdelhamid and Takemori, 1991; Bhargava, 1991a; Bhargava et al., 1991a,b; Bhargava and Gulati, 1990a; Rothman et al., 1991), several selective and nonselective opioid receptor antagonists have been used to counteract morphine tolerance and physical dependence processes. Orahovats et al. (1953) reported that in rats the degree of tolerance to morphine was partially inhibited when morphine was administered together with nalorphine. A similar effect of nalorphine was observed in humans (Eddy et al., 1960) and in monkeys (Seevers and Deneau, 1963). Mushlin and Cochin (1976) showed that naloxone injected 35 min after morphine pretreatment prevented the development of tolerance to morphine in the rat. Similarly, when given at 5 min, 3 h, or 24 h, naloxone (0.8 mg/kg, i.p.) prevented the development of acute tolerance to morphine induced by injecting the drug (30 mg/kg, i.p.). The analgesic response to morphine (15 mg/kg) was tested 48 h after initial morphine injection by using a shock threshold test (Kesner and Priano, 1977). The inhibition by naloxone of morphine-induced tolerance and dependence in mice was dose and time dependent. Such an effect was observed whether the tolerance was induced by injection of a single large dose of morphine (100 mg/kg, s.c.) or when morphine was injected on a chronic basis using a slow-release preparation (Yano and Takemori, 1977). Similarly, the importance of the timing of administration of the antagonist for the inhibition of the development of dependence on morphine has been demonstrated in mice and rats (Tremblay et al., 1976). The dose-response curves for the antagonism by naloxone of morphine-induced analgesia and dependence appeared to be parallel (Smits, 1976). Naltrexone, a long-acting opioid receptor antagonist that can be administered orally, has been used in rehabilitation of narcotic addicts (Resnick et al., 1977). Experiments have been carried out to study the effects of naltrexone on the development of physical dependence on morphine. A single i.p. injection of naltrexone (20 mg/kg) partially inhibited the development of physical dependence on morphine in mice rendered dependent by pellet implantation for 3 days. The effect of naltrexone was much more pronounced when given prior to and during the development of dependence. The effect was also seen when naltrexone was injected 1 day after the pellet implantation (Bhargava, 1978a). A single pellet of naltrexone containing 10 mg of the drug completely blocked the tolerance to the analgesic and hyperthermic effects of morphine and also the development of physical dependence on morphine in the rat. In this study, the tolerance/dependence was induced by s.c. implantation of 6 morphine pellets (75 mg each) during a 7-day period (Bhargava et al., 1994a).

b. SPECIFIC OPIOID RECEPTOR ANTAGONISTS. It has been shown that μ-opioid receptors are down-regulated in the brain of morphine-tolerant or -dependent rats (Bhargava and Gulati, 1990a) and guinea pigs (Werling et al., 1989). However, in mice and rats, others have shown that μ-opioid receptors are up-regulated (Abdelhamid and Takemori, 1991; Rothman et al., 1991). β-Funaltrexamine (fig. 3a), a highly selective μ-opioid receptor antagonist (Ward et al., 1982), has been shown to inhibit the development of physical dependence on morphine in rats and monkeys (Aceto et al., 1986). Similarly, conflicting reports exist concerning the involvement of δ- and κ-opioid receptors in morphine tolerance and dependence (Bhargava, 1991a). The δ-receptor antagonists, naltrindole (fig. 3b) and its analog, naltrindole 5′-isothiocyanate (fig. 3b), inhibited the tolerance to and physical dependence on morphine induced by either injection of a single dose of morphine or by pellet implantation procedure in mice. These δ-opioid receptor antagonists, unlike μ-opioid receptor antagonists, did not alter the analgesic response to morphine (Abdelhamid et al., 1991), and thus further studies are warranted not only to understand the role of opioid receptors in the tolerance/dependence processes but also to develop more selective δ-opioid agonists to counteract these processes.

Physical dependence on butorphanol has been shown to be inhibited by δ- and κ-opioid receptor antagonists. Treatment with a δ-opioid receptor antagonist, naltrindole, or a κ-opioid receptor antagonist, nor-binaltorphim-

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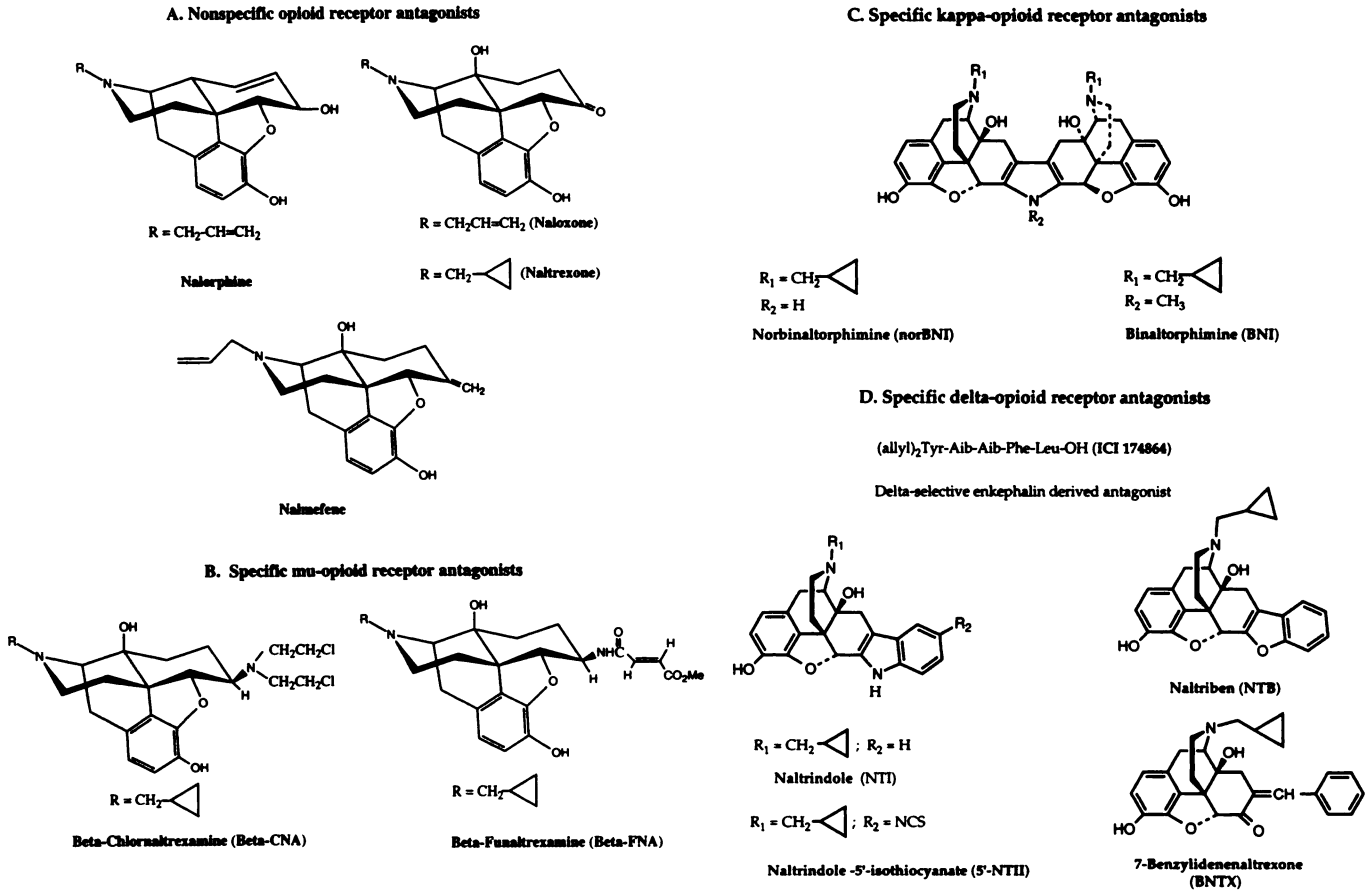

FIG. 3. Structures of opioid receptor antagonists.

ine, 3 h before and 24 and 48 h after the commencement of i.c.v. infusion of butorphanol (26 nmol/h) inhibited the development of physical dependence on butorphanol. Thus, highly selective opioid receptor antagonists may be useful in counteracting the development of physical dependence on mixed opioid receptor agonist-antagonists.

c. κ-OPIOID RECEPTOR AGONISTS. Several studies suggest that μ- and κ-opioid receptor agonists behave as antagonists to each other. Dynorphin (1–13), an endogenous ligand for the κ-opioid receptor (Goldstein et al., 1979; Oka et al., 1982) when administered i.c.v., was shown to inhibit morphine and β-endorphin analgesia in morphine-naive mice (Tulunay et al., 1981). Similar effects were reported with dynorphin (1–17) administered i.t. on morphine-induced analgesia in rats (Schmauss and Herz, 1987). Bremazocine (Römer et al., 1980) and U-50,488H (Lahti et al., 1982; Von Voigtlander et al., 1983), two exogenous κ-opioid receptor agonists, also antagonize morphine-induced analgesia in morphine-naive rats (Ramarao et al., 1988). Finally, U-50,488H antagonizes μ-opioid receptor-mediated inhibition of nociceptive neurons in the rat dorsal horn (Dickenson and Knox, 1987). With these results in mind, studies were undertaken to determine whether morphine-induced tolerance can be modified by κ-opioid receptor agonists. The development of tolerance to morphine in the mouse has been shown to be blocked by i.p. or i.t. injections but not i.c.v. injections of U-50,488H, a κ-opioid receptor agonist. The suppressive action of U-50,488H on morphine tolerance was antagonized by norbinaltorphimine (fig. 3b), a κ-opioid receptor antagonist when given i.p. or i.t. but not by the i.c.v. route of administration. These studies indicate a role for κ-opioid receptors in morphine tolerance (Takahashi et al., 1991). A similar effect of U-50,488H has been demonstrated in the rat (Yamamoto et al., 1988). However, studies in our laboratory showed that U-50,488H (25 mg/kg) given i.p. twice daily did not block tolerance to the analgesic or hyperthermic effect of morphine in the rat treated by either implanting four pellets during a 3-day period or six pellets during a 7-day period (Bhargava et al., 1991d). Similarly, the binding of [^{3}H]ethylketocyclazocine or [^{3}H]U-69,593 to brain regions and spinal cord of morphine-tolerant and -abstinent rats was shown to be unaltered (Bhargava et al., 1991b). Our results are in agreement with the studies of Fukagawa et al. (1989) who showed that U-50,488H does not affect the development of morphine dependence in the rat. The disparity between the above studies may be due to the method used to induce morphine tolerance. In

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our laboratory, tolerance to morphine was induced by pellet implantation, whereas in the other studies, daily injections of morphine were given. However, several studies have shown that endogenous or exogenous κ-opioids restore the actions of morphine in morphine-tolerant animals (Dickenson and Knox, 1987; Ramarao et al., 1988; Rezvani and Way, 1984; Schmauss and Herz, 1987; Tulunay et al., 1981). The mechanisms of such actions have not yet been delineated.

2. Opioid peptides. a. ENKEPHALINS. Soon after the discovery of opioid receptors in the mammalian brain, two pentapeptides, leucine-enkephalin (Tyr-Gly-Gly-Phe-Leu) and methionine-enkephalin (Tyr-Gly-Gly-Phe-Met) were isolated and found to have morphine-like activity in various assay systems (Bhargava, 1977a, 1978b; Belluzzi et al., 1976; Buscher et al., 1976; Hughes et al., 1975; Pasternak et al., 1976). These endogenous substances could modulate or regulate the acute and chronic actions of exogenous opioids. The enkephalins have been shown to modify the analgesic action of morphine (Lee et al., 1980). The effects of leucine- and methionine-enkephalin on tolerance and dependence on morphine were determined in mice. The tolerance/dependence was induced by s.c. injection of a single dose (100 mg/kg) of morphine. The tests for tolerance or dependence were performed 3 h after the injection of morphine. Enkephalins were administered i.p. 15 min after morphine (100 mg/kg) administration. Leucine-enkephalin (5 mg/kg) enhanced not only the analgesic potency of morphine but also the development of tolerance to morphine, as evidenced by increases in the ED_{50} values of morphine for the analgesic response. Similarly, the development of physical dependence was enhanced as evidenced by a decrease in the ED_{50} value of naloxone for the jumping response. Methionine-enkephalin, on the other hand, did not affect either morphine analgesia or the development of tolerance and dependence processes (Vaught and Takemori, 1979). Also, studies in Way's laboratory (Chapman et al., 1980) showed that leucine-enkephalin had no effect on morphine analgesia, tolerance, or dependence development in mice. Low doses of methionine-enkephalin (i.c.v.) antagonized morphine analgesia without affecting tolerance or dependence development. The reasons for the discrepancy between the studies of Vaught and Takemori (1979) and Chapman et al. (1980) are not apparent at this time. The studies of Chapman et al. (1980) were carried out with peptides obtained from three sources and on several strains of mice. Therefore, it is unlikely that the purity of the peptide and specific strain of mice are the factors in the different results obtained from the two laboratories.

b. DYNORPHINS. Dynorphin A contains the 17-amino acid peptide sequence that was isolated from porcine pituitary and duodenum extracts (Goldstein et al., 1981) and commences with leucine-enkephalin at the NH_2 terminus. Its four COOH-terminal residues (Trp-Asp-Asn-Gln) do not appear to be necessary for its activity at the opioid receptors because dynorphin (1–13) produces actions similar to those of dynorphin (1–17) (Goldstein et al., 1979). Although dynorphins (fig. 4) have preferential action at the κ-opioid receptor, they also bind to μ- and δ-opioid receptors (Corbett et al., 1982).

Dynorphin A (1–13) administered i.v. in doses of 2.5 and 5.0 μmol/kg inhibited the expression of morphine withdrawal and tolerance in mice (Takemori et al., 1992). A morphine pellet was implanted in mice for 3 days. Dynorphin A (1–13) was injected 5 min prior to injection of naloxone. Dynorphin A (1–13) increased the naloxone ED_{50} for the jumping response. The ED_{50} value of morphine for the analgesic response in morphine-tolerant mice was also increased. This increase was reversed in a dose-dependent manner by dynorphin A (1–13). These results are analogous to the earlier studies from the same laboratory, where dynorphin A (1–13) was shown to suppress naloxone-precipitated withdrawal and enhance the analgesic action of morphine in morphine-tolerant animals (Aceto et al., 1982; Tulunay et al., 1981). Similar effects have been reported for dynorphin A (2–17) and dynorphin A (2–11) (Takemori et al., 1993). It should be noted that the latter two compounds are devoid of tyrosine in position 1 of the dynorphin A (1–17) molecule and does not possess opioid actions or bind to opioid receptors (Chavkin and Goldstein, 1981; Walker et al., 1982). Although the mechanism by which dynorphin and its analogs modify morphine effects is not clear, studies in our laboratory have demonstrated that morphine tolerance and abstinence are associated with increases in the levels of dynorphin A (1–13) in several brain regions but decreases in the spinal cord (Rattan et al., 1992). In particular, a long-lasting depletion of dynorphin A (1–13) levels was found in the spinal cord of morphine-tolerant and -dependent rats. This may partially explain the efficacy of i.t. administration but not of i.c.v. administration of dynorphin A (1–13) in the modification of the expression of morphine tolerance and withdrawal.

B. Nonopioid Peptides

1. Thyrotropin-releasing hormone. TRH, a tripeptide (pGlu-His-Pro-NH_2), in addition to its endocrine activity of releasing thyrotropin and prolactin (Bowers et al., 1971), also possesses many pharmacological actions in the CNS. TRH potentiates the actions of levodopa in hypophysectomized or thyroidectomized animals (Plotnikoff et al., 1972, 1974). Similarly, TRH antagonizes

Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ileu-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln

Dynorphin A (1-17)

Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ileu-Arg-Pro-Lys-Leu-Lys

Dynorphin A (1-13)

Gly-Gly-Phe-Leu-Arg-Arg-Ileu-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln

Dynorphin A (2-17)

FIG. 4. Structures of dynorphins.

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the sedative and hypothermic actions of CNS depressants, including morphine, but it does not antagonize the analgesic effect of morphine or β-endorphin (Bhargava et al., 1983; Holaday et al., 1978; Horita et al., 1976). Studies in this laboratory have shown that TRH (4–16 mg/kg, s.c.) prevents the development of tolerance to the analgesic but not to the hypothermic actions of morphine in mice and rats (Bhargava, 1981e; Ramarao and Bhargava, 1990a). Similarly, TRH inhibits the development of physical dependence in mice as evidenced by the inhibition of hypothermic response observed during abrupt and naloxone-induced withdrawal. However, the stereotyped jumping response could not be blocked (Bhargava, 1980a). This indicates that tolerance to and physical dependence on morphine can be modified by TRH, although its mechanism of action is not understood. Chronic administration of morphine, however, does not affect spinal cord or brain TRH receptors but down-regulates pituitary TRH receptors (Bhargava et al., 1989a; Rahmani et al., 1990). It should also be noted that TRH does not affect morphine analgesia (Bhargava, 1981e), nor does it modify the binding of ^{3}H-ligands to opioid receptors in the brain (Das and Bhargava, 1987a,b; Martin et al., 1977). However, κ-opioid receptor agonists and antagonists selectively inhibit the binding of [^{3}H] methyl-TRH to brain membranes (Bhargava et al., 1988; Bhargava and Das, 1986; Das and Bhargava, 1987a,b). Therefore, it appears that the inhibition of morphine tolerance and physical dependence by TRH may involve mechanisms other than those associated with opioid receptors.

2. *Calcitonin.* Calcitonin, a peptide containing 32 amino acids, secreted by the parafollicular C-cells of the thyroid gland, produced analgesia in rabbits following i.c.v. injections (Pecile et al., 1975) which was not mediated via opioid receptors because it was not antagonized by levallorphan (Yamamoto et al., 1979). Concurrent i.m. administration of an analog of eel calcitonin ([Asu^{1,7}] eel calcitonin) with morphine inhibited the development of physical dependence on morphine but tolerance development was not modified (Clementi et al., 1989). Thus, calcitonin is another example of a drug that can separate the processes of the development of tolerance and physical dependence.

3. *Melanocyte-stimulating hormone release-inhibiting factor and analogs.* The hormones of the posterior pituitary, vasopressin and oxytocin, and their analogs elicit a variety of actions on the CNS. Some of them include facilitation of conditioned avoidance behaviors in intact and hypophysectomized rats and have been reviewed (Bhargava, 1986a). Several of the analogs of vasopressin and oxytocin (Figs. 5 and 6) were shown to facilitate the development of tolerance and physical dependence on morphine in mice (Krivoy et al., 1974) and rats (van Ree and deWied, 1976). The doses of the peptides used were 50 μg (mouse) and 1 μg (rat) given s.c. Morphine was

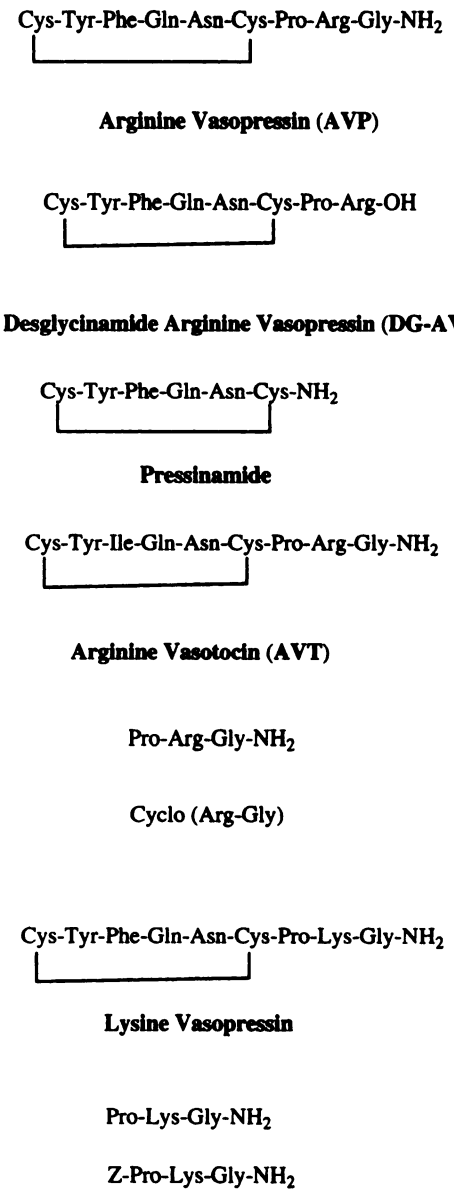

FIG. 5. Structures of arginine and lysine vasopressin and their COOH-terminal fragments.

given by multiple injections, and analgesia was measured by the hot plate test. Some of the earlier work and inconsistencies have been studied and summarized (Bhargava, 1986a). Studies in our laboratory have shown that the COOH-terminal peptides of oxytocin, Pro-Leu-Gly-NH$_2$ (MIF) and its synthetic analogs, cyclo (Leu-Gly) and other analogs (fig. 7), were effective in inhibiting tolerance to morphine in mice and rats.

The majority of our studies has been done with MIF and cyclo (Leu-Gly). We were unable to show the facilitation of morphine tolerance with MIF (Bhargava, 1980d). On the other hand, we demonstrated that these peptides blocked the tolerance to analgesic, cataleptic, hypothermic, and locomotor depressant effects of morphine (Bhargava, 1980c, 1981a,b, 1982a; Bhargava et al., 1980; Bhargava and Kim, 1982), β-endorphin (Bhargava, 1981c), and buprenorphine (Bhargava, 1982b), as well as

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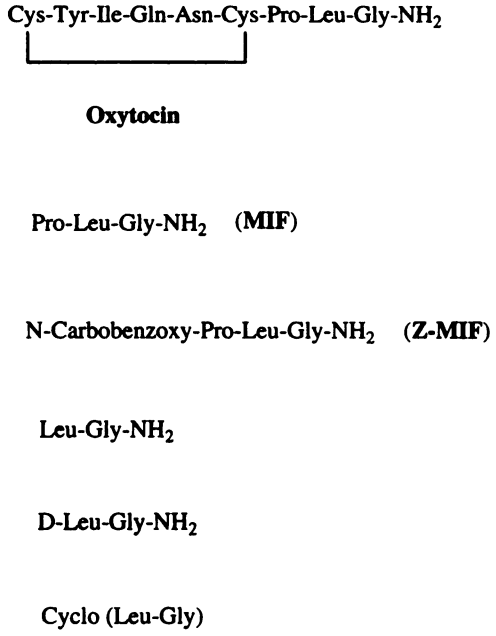

FIG. 6. Structures of oxytocin, MIF, and analogs of MIF.

physical dependence on morphine (Ritzmann et al., 1979; Walter et al., 1978, 1979). Further studies revealed that intragastric administration of MIF and cyclo (Leu-Gly) can block tolerance to the analgesic effect of morphine in the rat (Bhargava, 1988; Bhargava and Ramarao, 1989a). Our studies with Z-Pro-D-Leu on morphine dependence and with cyclo (Leu-Gly) on morphine tolerance have been confirmed by several investigators (Burton et al., 1991; Kovacs et al., 1981). In fact, Burton et al. (1991) showed that cyclo (Leu-Gly) can also inhibit the tolerance to the respiratory depressant action of morphine in the rat.

ACTIVE ANALOGS	INACTIVE ANALOGS
Pro-Leu-Gly-NH_2 (MIF)	Δ^3-Pro-Leu-Gly-NH_2
Z-Pro-Leu-Gly-NH_2 (Z-MIF)	Z-Pro-Leu-Gly-$N(CH_3)_2$
Z-Gly-Pro-Leu-Gly-COOH	Z-Pro-Leu-Gly-COOH
Glu-Leu-Gly-NH_2	Z-Leu-Gly-NH_2
Pro-Leu	Z-Pro-Leu-NH_2
Z-Pro-Leu	Z-Pro-Gly
Z-D-Pro-D-Leu	Z-Pro-Ala
Z-Pro-D-Leu	Z-Pro-D-Ala DCHA*
Z-Pro-Gln	Z-Pro-Ile
Z-Pro-Ser	Z-Pro-Val
Z-Pro-Met	Z-Pro-Glu
Z-Pro-ΔPhe	Z-Ala-Pro
Z-Pro-Tyr	Z-Pro-Phe
Cyclo (Leu-Gly)	Cyclo (Leu-Ala)
Cyclo (Pro-Phe)	Cyclo (Pro-D-Leu)
*Dicyclohexylamine	

FIG. 7. Structures of active and inactive analogs of Pro-Leu-Gly-NH_2 (MIF) used to block morphine tolerance and dependence in mice.

Although the mechanism by which MIF and its analogs produce their inhibiting action on tolerance to opioids is not evident, it is clear that they (*a*) enhance the binding of dopamine agonists such as [^{3}H]apomorphine in the brain (Bhargava, 1983b), (*b*) do not affect the binding of μ-, δ-, or κ-ligands to brain membranes (Bhargava et al., 1983), (*c*) inhibit the supersensitivity of dopamine receptors induced by morphine or β-endorphin (Bhargava, 1981d, 1983a; Das and Bhargava, 1985; Ritzmann et al., 1979), (*d*) do not interact with cholinergic muscarinic receptors (Das and Bhargava, 1986), (*e*) produce their effects through the formation of active metabolites (Bhargava, 1986b), (*f*) antagonize the actions of κ-opioid receptor agonists (Bhargava and Ramarao, 1989b), and (*g*) inhibit or reverse the changes in cyclic guanosine 5′-monophosphate phosphodiesterase activity induced by morphine in the brain (Burton et al., 1991). Thus, even though the mechanisms in opioid-induced tolerance/dependence processes and in the action of peptides inhibiting these processes are not understood, further studies are required to determine the actions of orally effective peptides.

It was of interest to determine whether MIF-related peptides affect the tolerance induced by κ-opioid receptor agonists. Cyclo (Leu-Gly) was shown to antagonize the acute actions of U-50,488H but did not modify the tolerance to its analgesic action. The inhibitory effect of cyclo (Leu-Gly) on the actions of U-50,488H was not mediated via κ-opioid receptors because it did not affect the binding of [^{3}H]ethylketocyclazocine to brain membranes (Bhargava and Ramarao, 1989b). These studies suggest that the mechanisms by which μ- and κ-opioid produce tolerance are different, the former being modified by cyclo (Leu-Gly), whereas the latter was not affected.

4. Cholecystokinin and its analogs. The gut peptide CCK also occurs in the brain, the most abundant form being the sulfated octapeptide, which is believed to act as a neuromodulator or neurotransmitter. CCK-containing neurons and CCK-A and CCK-B receptors appear to be located in brain areas such as basal ganglia, amygdala, and hypothalamus (Hughes et al., 1991). Considerable evidence suggests that CCK interacts with opioid receptors in pain mechanisms. Although large doses (≥50 μg/kg) of CCK induce naloxone-reversible analgesia (Jurna and Zetler, 1981), small doses (3 to 16 μg/kg) of the drug inhibit the analgesic action of opioids in rodents (Faris et al., 1983). The weak nonselective CCK receptor antagonist, proglumide, and the potent CCK receptor antagonist, L-364,718 [1-methyl-3-(2-indoloyl) amino-5-phenyl-^{3}H-1, 4-benzodiazepin-2-one], potentiate morphine-induced analgesia and prevent the development of tolerance to morphine in the rat (Dourish et al., 1988; O'Neill et al., 1989; Watkins et al., 1984). Similar enhancement of morphine analgesia and prevention of tolerance to systemically administered morphine has been demonstrated in the rat by CCK-B receptor antagonist L-365,260 (Dourish et al., 1990).

Several lines of evidence suggest that CCK is released in response to activation of opioid receptors by morphine in the spinal cord. Morphine administered i.t. causes the release of CCK from the spinal cord (Tang et al., 1984a). CCK administered i.t. inhibits the depressive effect of morphine on the nociceptive flexion reflexes (Wiesenfeld-Hallin and Duranti, 1987), and spinal application of CCK attenuates morphine-induced inhibition of C-fiber-

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evoked discharges of dorsal horn nociceptive neurons (Kellstein et al., 1991). The release of CCK is selectively controlled by δ-opioid receptors (Benoliel et al., 1992; Ruiz-Gayo et al., 1992). The management of clinical pain by administering opioids by the i.t. or epidural route has become important (Bromage et al., 1980; Wang et al., 1979), but tolerance develops to the analgesic effect of spinally administered opioids (Ventafridda et al., 1979). The effect of i.t. administration of proglumide on tolerance to morphine induced by i.t. injection in the rat has been studied (Kellstein and Mayer, 1991). The spinal coadministration of lorglumide or proglumide for 6 days prevented the tolerance to i.t. administered morphine in the rat. The tolerance induced by a higher dose of morphine (3 μg) required higher doses of the CCK receptor antagonists, whereas a lower dose of the antagonist was required when tolerance was induced by a 1-μg dose of the drug. Thus, CCK antagonists may prove to be useful adjuncts to opioids in the management of chronic pain.

5. Phe-Met-Arg-Phe-NH_2-like peptides. The tetrapeptide FMRF-NH_2, isolated from macrocallista nimbosa ganglia (Price and Greenberg, 1977), appears to be present in the CNS of mammals, with the highest concentration in the hypothalamus and spinal cord (Dockray and Williams, 1983). The amino acid sequence Phe-Met-Arg-Phe is present in the opioid heptapeptide Tyr-Gly-Gly-Phe-Met-Arg-Phe (metenkephalin-Arg^6-Phe^7); however, immunohistochemical studies suggest that the location of the two peptides is different, and therefore FMRF-NH_2 may not be derived from metenkephalin-Arg^6-Phe^7 (Weber et al., 1981). FMRF-NH_2-like immunoreactivity is released from the spinal cord when morphine is added to the artificial spinal fluid perfusing the subarachnoid space of the rat (Tang et al., 1984b). FMRF-NH_2 injected i.t. antagonizes the analgesic action of morphine given i.c.v. or of metenkephalin-Arg^6-Phe^7-NH_2 given i.t. Additionally, IgG, prepared from a specific FMRF-NH_2 antiserum, produced a naloxone-reversible analgesia. Anti-FMRF-NH_2 IgG given every 4 h inhibited the development of tolerance to the analgesic effect of morphine when the latter was induced by eight successive injections 2 h apart (Tang et al., 1984b).

Another peptide, Phe-Leu-Gln-Pro-Gln-Arg-Phe-NH_2, has been suggested by Yang et al. (1985) to be another endogenous antiopioid peptide. This peptide has also been referred to as F-8-F-amide, or NPFF (Lake et al., 1991). NPFF levels in cerebrospinal fluid of morphine tolerant/dependent rats were found to be increased (Malin et al., 1990a). In morphine-tolerant rats, intraventricular injection of IgG from NPFF antiserum was shown to restore the analgesic response to i.c.v. morphine, indicating that the state of morphine tolerance is reversed (Lake et al., 1991).

C. Drugs Affecting Neurotransmitter Receptor Systems

The role of several neurotransmitter receptor systems in morphine tolerance and abstinence has been studied. They include serotonin, dopamine, GABA-benzodiazepine, adenosine, aspartate, and excitatory amino acid receptors. The evidence for the possible involvement of these transmitters in the chronic action of morphine is based on the changes induced in the function of receptors and the modifications of tolerance and physical dependence on morphine by drugs that alter the activity of the neurotransmitter systems.

1. Serotonin. Earlier studies from Way's laboratory suggested that chronic administration of morphine to mice was associated with increased turnover of 5-HT in the brain (Way et al., 1968). Furthermore, inhibitors of 5-HT synthesis, such as *p*-chlorophenylalanine, or selective neurotoxin for 5-HT, such as 5,6-dihydroxytryptamine, inhibited the development of tolerance and physical dependence on morphine in mice (Ho et al., 1972, 1973a). Conversely, concurrent injections of tryptophan, a precursor for the synthesis of 5-HT, enhanced tolerance and physical dependence development (Ho et al; 1975). Other investigators, however, have not been able to confirm these findings (Cheney and Goldstein, 1971; Marshall and Grahame-Smith, 1971).

Multiple receptors for 5-HT have been identified, namely, 5-HT_1, 5-HT_2, and 5-HT_3 (Hoyer and Schoeffter, 1991). Further subclassification has been done for 5-HT_1 receptors, such as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, and 5-HT_{1D}. However, the physiological role for each subtype of 5-HT receptors is not clear. The studies from this laboratory suggest that tolerance to morphine is associated with up-regulation of 5-HT_2 receptors of certain brain regions, whereas abstinence from morphine causes up-regulation of central 5-HT_1 receptors in the rat (Gulati and Bhargava, 1988, 1989).

There are several other procedures by which the central 5-HT activity can be altered. Thus, *d*-fenfluramine, a 5-HT releaser, and metergoline, a central 5-HT receptor antagonist, when administered concurrently with morphine, increased and decreased, respectively, the development of physical dependence in the rat as evidenced by changes in the jumping behavior (Samanin et al., 1980a). Inhibition in the development of physical dependence on morphine in the rat was also observed with cyproheptadine, a 5-HT antagonist (Cervo et al., 1981). The effect of chronic administration and withdrawal of U-50,488H on central 5-HT_1 and 5-HT_2 receptors was determined in the rat. Chronic treatment with U-50,488H was associated with an up-regulation of cerebral cortical 5-HT_1 receptors (Gulati et al., 1989) and down-regulation of hypothalamic 5-HT_{1A} receptors (Veeranna et al., 1992). The effects of drugs acting on 5-HT systems on the tolerance to κ-opioid receptor agonists still need to be determined.

2. Catecholamines. Whereas the role of catecholaminergic systems in the development of tolerance to morphine appears to be minimal, they play an important role in the abstinence syndrome. Chronic administration of

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morphine to rats by the pellet implantation procedure resulted in the development of tolerance to its analgesic action. The binding characteristics of ^{3}H-ligands for dopamine D_1 and D_2 receptors were determined in brain regions and spinal cord of morphine-tolerant rats from which the pellets had not been removed, i.e., they were not undergoing abstinence syndrome. The B_{max} and K_d values of [^{3}H]SCH 23390 (dopamine D_1 receptor antagonist) and [^{3}H]spiroperidol (dopamine D_2 receptor antagonist) to bind to brain regions and spinal cord of morphine-tolerant rats were unaltered (Bhargava and Gulati, 1990b; Reddy et al., 1993).

The effect of drugs affecting catecholamines in the CNS on the development of tolerance and physical dependence has also been determined. The effect of 6-hydroxydopamine, which is known to deplete catecholamines selectively by destruction of catecholaminergic neurons, was investigated in mice rendered tolerant to and physically dependent on morphine by pellet implantation. Pretreatment with 6-hydroxydopamine intracerebrally with a dose that caused 66 and 30% depletion of brain norepinephrine and dopamine, respectively, reduced the analgesic response of morphine in both tolerant and nontolerant mice but did not affect the development of tolerance to morphine. However, the development of physical dependence on morphine was enhanced by 6-hydroxydopamine treatment as evidenced by increased incidence of jumping following injection of naloxone and increased weight loss after abrupt withdrawal (Friedler et al., 1972). Similar effects of 6-hydroxydopamine were reported in the rat (Bhargava et al., 1973).

The effect of inhibition of dopamine β-hydroxylase by 1-phenyl-3-(2-thiazolyl)-2-thiourea on morphine-induced analgesia, tolerance, and physical dependence was determined in the mouse (Bhargava and Way, 1974). Administration of 1-phenyl-3-(2-thiazolyl)-2-thiourea decreased the concentration of norepinephrine and dopamine in the brain and inhibited the development of tolerance and physical dependence on morphine.

Bromocryptine, a specific dopamine D_2 receptor agonist, was shown to potentiate morphine analgesia and suppress the development of tolerance to the analgesic action of morphine (Gomaa et al., 1989).

Tolerance to U-50,488H induced by multiple injections in the rat on the binding of [^{3}H]SCH 23390 and [^{3}H] spiroperidol to brain regions and spinal cord was also determined and was found to be unaffected (Bhargava et al., 1991c; Veeranna et al., 1993). Much more work needs to be done on the effect of highly selective dopamine receptor agonists and antagonists on the development of tolerance to and physical dependence on μ- and κ-opioid receptor agonists.

3. γ-Aminobutyric acid-benzodiazepine. Administration of GABA has been shown to facilitate the development of tolerance to and physical dependence on morphine in mice (Ho et al., 1976). Elevation of brain levels of GABA by inhibiting its metabolism by aminooxyacetic acid enhanced the development of tolerance and physical dependence. On the other hand, blockade of postsynaptic GABA receptors by bicuculline resulted in an inhibition of tolerance and dependence development (Ho et al., 1976). Chronic administration of morphine has been shown to modify central GABA receptors (Ticku and Huffman, 1980).

Midazolam, a benzodiazepine receptor agonist, administered i.p. (0.03 to 3 mg/kg) daily for 11 days attenuated the development of tolerance to the analgesic action of morphine. Midazolam also attenuated a decrease in weight gain induced by chronic injections of morphine and also inhibited naloxone-precipitated jumping behavior in morphine-dependent rats (Tejwani et al., 1993). These studies suggest that the development of both tolerance and physical dependence are inhibited by benzodiazepine receptor agonists.

4. Adenosine. Adenosine receptors have been classified as A_1 or A_2 depending on whether they inhibit (A_1) or stimulate (A_2) the accumulation of cAMP (Van Calker et al., 1979). The effects of an adenosine receptor agonist, PIA, and antagonist, caffeine, on nociception and morphine-induced analgesia, tolerance, and physical dependence were studied in mice (Ahlijanian and Takemori, 1985). PIA, an adenosine A_1 receptor agonist, produced analgesia in both the tail-flick and the acetic acid writhing assays. The analgesic action of PIA was antagonized by caffeine in a noncompetitive manner. PIA potentiated morphine-induced analgesia, tolerance, and dependence. The effects of PIA were antagonized by caffeine. Thus, the adenosine receptor agonist facilitates, whereas the adenosine receptor antagonist can inhibit the actions of morphine (Ahlijanian and Takemori, 1985).

5. Aspartate. The effect of aspartic acid on morphine tolerance and physical dependence has been determined in the rat (Koyuncuoglu et al., 1977). Rats were given morphine in drinking water for 30 days. At the end of this period, some rats were given aspartic acid and the others were given the vehicle. In another set of rats, aspartic acid was administered concurrently with morphine. Aspartic acid prevented the development of tolerance to the analgesic effect of morphine as well as physical dependence as evidenced by the inhibition of body weight loss.

6. Excitatory amino acids. Recent evidence suggests that the excitatory amino acid receptor systems, namely, NMDA, quisqualate, and kainate (Monaghan et al., 1989) may be involved in pain and opioid tolerance/dependence mechanisms. These excitatory amino acids produce analgesia when microinjected into the periaqueductal gray matter (Jacquet, 1988). The NMDA receptor antagonist, [(+)-5-methyl-10,11-dihydro-5H-dibenzo-(a,d)cyclohepten-5,10-imine] (MK-801) (fig. 8),

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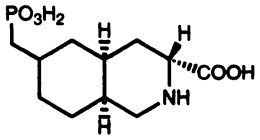
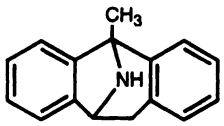
Competitive NMDA receptor antagonist



LY274614

Noncompetitive NMDA receptor antagonist



Dizocilpine (MK-801)

FIG. 8. Structures of typical NMDA receptor antagonists.

has been shown to either block (Lipa and Kavaliers, 1990) or produce no effect (Bhargava and Matwyshyn, 1993; Marek et al., 1991) on morphine analgesia. Both kynurenic acid, a wide-spectrum excitatory amino acid receptor antagonist, and the specific NMDA receptor antagonist, MK-801, were shown to inhibit the development of tolerance to the analgesic effect of morphine in the rat (Marek et al., 1991). The tolerance to morphine was induced by daily injections of drug (15 mg/kg) for 4 days. The doses of kynurenic acid and MK-801 were 150 and 0.05 mg/kg, respectively, and were given 20 min prior to morphine injection. At the end of the tolerance induction period, analgesia was measured by using the hot plate test. Similar findings with MK-801 (0.03 to 3.0 mg/kg) were reported in rats made tolerant by injecting morphine (10 mg/kg day) for 9 days. In addition, the escape jumps following naloxone injection were also blocked. Thus, both tolerance and physical dependence were attenuated by MK-801, although high doses, 0.3 and 3.0 mg/kg, produced severe toxicity and death (Trujillo and Akil, 1991). Studies in our laboratory have utilized implantation of six morphine pellets during a 7-day period procedure to induce tolerance to morphine in the rat. When injected once or twice a day, MK-801 (0.03 to 0.3 mg/kg, i.p.) inhibited the tolerance to the analgesic but not to the hyperthermic effect of morphine. In once a day MK-801 treatment, there was no dose-dependent effect, but in twice a day treatment, it was dose dependent. However, in both cases, increased mortality was observed with increasing doses of MK-801 (Bhargava and Matwyshyn, 1993). There also appear to be some specific differences in the actions of MK-801 in mice and rats. Whereas Marek et al. (1991) and Trujillo and Akil (1991) showed blockade of morphine tolerance by MK-801 in the rat without modifying the acute analgesic response, recent studies in mice showed that both morphine-induced analgesia and tolerance were antagonized by MK-801. This effect of MK-801 was not related to its opioid receptor antagonistic action because the IC_{50} for inhibiting the binding of [^{3}H]naloxone was 34 μM (Lutfy et al., 1993).

It should be noted that MK-801 is a selective antagonist at the NMDA subtype of amino acid receptor where it noncompetitively blocks the NMDA receptor-operated ion channel. Additionally, MK-801 and other noncompetitive NMDA receptor antagonists produce PCP-like behaviors in animals (Willetts et al., 1990; Rasmussen et al., 1991). On the other hand, competitive NMDA receptor antagonists act at the glutamate recognition site which appears to be distinct from that of MK-801 (Schoepp et al., 1991) and do not show PCP-like behaviors (Rasmussen et al., 1991). LY 274614 (6-phosphonomethyl-decahydro-isoquinoline-3-carboxylic acid) (fig. 8) is a potent competitive NMDA receptor antagonist (Leander and Ornstein, 1990; Ornstein et al., 1990; Schoepp et al., 1991). LY 274614 (fig. 8) has been shown to inhibit antagonist-induced withdrawal symptoms in morphine-dependent rats without producing the PCP-like behaviors (Rasmussen et al., 1991). The effect of LY 274614 on tolerance to the analgesic effect of morphine was determined in the rat by using the hot plate test. LY 274614 given by continuous s.c. infusion attenuated the tolerance to morphine induced by twice daily injections of morphine (10 mg/kg, s.c.) (Tiseo and Inturrisi, 1993). Interestingly, 1 week after the termination of treatment, the LY 274614-treated rats maintained the analgesic efficacy of morphine, whereas the control rats remained tolerant to morphine. These studies suggest that the competitive NMDA receptor antagonists that are devoid of PCP-like behavior may be preferable over the noncompetitive NMDA receptor antagonists such as MK-801.

Studies in our laboratory indicate that in morphine-tolerant and -abstinent rats, the binding of [^{3}H]MK-801 in the presence of glutamate and glycine is decreased in some brain regions (Bhargava et al., 1994c; Gudehithlu et al., 1993); however, in the absence of glutamate and glycine, the binding of [^{3}H]MK-801 decreases modestly only in the cortex (Gudehithlu et al., 1994). This suggests that the activity of endogenous glutamate and glycine is perhaps altered following the activation of NMDA receptor in chronic morphine-treated animals.

The effects of NMDA receptor antagonists on κ-opioid receptor agonist-induced analgesia and tolerance have also been examined in the rodents. MK-801 was shown to antagonize U-50,488H-induced analgesia in the rat (Kest et al., 1992). Studies in our laboratory have shown that MK-801 injected i.p. 10 min prior to the injections of U-50,488H dose-dependently inhibits the development of tolerance to the analgesic but not to the hypothermic action of U-50,488H in the rat. Multiple injections of U-50,488H were associated with decreased gain in body

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weight. Concurrent injections of MK-801 also inhibited the tolerance to U-50,488H but caused a further decrease in the body weight (Bhargava, 1994a). Similar effects are reported in mice (Bhargava and Thorat, 1994).

7. Calcium channel blockers. Because chronic treatment with morphine was shown to increase [^{3}H]nitrendipine (a calcium channel blocker, fig. 11) binding in mice and rats (Ramkumar and El-Fakahany, 1984, 1988), the effect of nifedipine, another calcium channel blocker on the analgesic response to morphine in nontolerant and morphine-tolerant rats, as well as on the development of tolerant and physical dependence on morphine, was determined. Nifedipine (5 mg/kg, i.p.) potentiated morphine-induced analgesia in the hot plate test but not in the tail-flick test in both nontolerant and morphine tolerant rats. In addition, concurrent administration of nifedipine with morphine did not modify tolerance development, but the physical dependence development was inhibited (Antikiewic-Michaluk et al., 1993). These studies demonstrated that the tolerance and physical dependence can be separated. There are many other instances in which similar conclusions have been reached. Further studies are necessary with other calcium channel blockers to determine the reasons for inactivity of nifedipine in potentiating morphine analgesia in the tail-flick test.

D. Drugs Modifying the Second-Messenger Systems

1. Cyclic 3′,5′-adenosine monophosphate. Administration of cAMP (10 mg/kg, i.v.) before and during morphine pellet implantation was shown to facilitate the development of tolerance and physical dependence in mice (Ho et al., 1973b). The enhancement in physical dependence was evidenced by the greater loss in body weight that occurred after abrupt withdrawal of morphine. It should be noted that cAMP antagonizes the analgesic response in both nontolerant and morphine-tolerant mice. The exact mechanism by which cAMP produces its effect on morphine analgesia, tolerance, and physical dependence is, however, not known. It should be noted that cAMP appears to modulate proenkephalin A gene expression (Folkesson et al., 1989).

2. Nitric oxide. It is clear from section III.C.6. that the NMDA receptor antagonist MK-801 attenuates tolerance to the analgesic action of morphine in the rat (Marek et al., 1991; Trujillo and Akil, 1991) and of U-50,488H in mice (Bhargava and Thorat, 1994) and rats (Bhargava, 1994b). Several of the NMDA effects are mediated via activation of NOS with subsequent release of nitric oxide, which in turn increases the formation of cyclic guanosine 5′-monophosphate (Bredt and Snyder, 1992). Nitric oxide has been recognized as a prominent neuronal second messenger, and its enzymatic formation from L-arginine has been demonstrated in cytosol obtained from rat forebrain synaptosomes (Knowles et al., 1989; Schmidt et al., 1989). The structures of several nitric oxide inhibitors are shown in figure 9. Recently, N^G-nitro-L-arginine, an inhibitor of NOS, was shown to prevent the development of tolerance to morphine in mice (Kolesnikov et al., 1992). Daily coadministration of N^G-nitro-L-arginine (8 mg/kg) with morphine (5 mg/kg, s.c.) prevented the development of tolerance to morphine in the mouse. The same authors showed that nitroarginine also reduces dependence but does not block tolerance to the analgesic action of U-50,488H, a κ-opioid receptor agonist in mice (Kolesnikov et al., 1993). However, studies in this laboratory clearly showed that NMMA (2 to 8 mg/kg, i.p.) blocked the tolerance to the analgesic and hypothermic actions of U-50,488H in the mouse. The tolerance to U-50,488H was induced by injecting the drug (25 mg/kg, i.p.) twice a day for 4 days. By itself, NMMA did not alter the analgesic and hypothermic actions of U-50,488H in naive mice (Thorat et al., 1993b). A similar inhibition of tolerance to the analgesic action of U-50,488H by NMMA has been reported in the rat (Bhargava, 1994b).

3. Pertussis toxin: role of guanosine 5′-triphosphate-binding proteins. The second-messenger system most commonly associated with opioid receptors involves inhibition of adenylate cyclase (Costa et al., 1983; Kurose et al., 1983; Sharma et al., 1975, 1977). Opioid receptor activation leads to opening of potassium channels in neurons of the CNS and inhibition of voltage-dependent calcium channels in primary cultures of dorsal root gan-

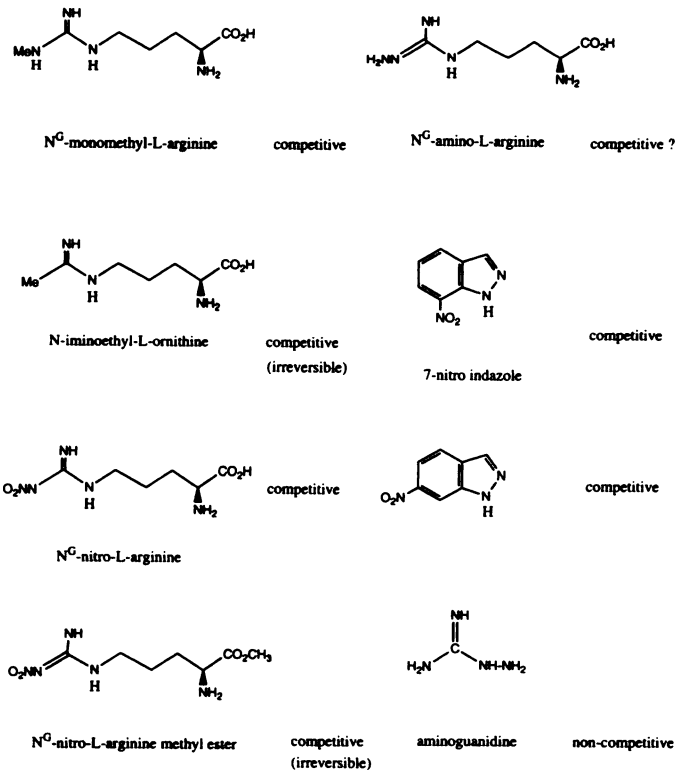

FIG. 9. Structures of competitive and noncompetitive inhibitors of NOS.

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glion (North, 1986). The control of ion channels and inhibition of adenylate cyclase are regulated by the G-proteins (Dolphin, 1987; Hescheler et al., 1987; Holz et al., 1986; Pfaffinger et al., 1985; Yatani et al., 1987). Pertussis toxin, which interferes with the G-protein-dependent mechanism, has been shown to inhibit morphine analgesia when injected in the rat spinal cord (Przewloci et al., 1987) or in the rat brain (Parenti et al., 1986; Parolaro et al., 1990). It also prevents opioid-induced dependence in the guinea pig ileum myenteric plexus (Lux and Schulz, 1986; Tucker, 1984). Six days after i.c.v. injection, pertussis toxin (0.5 μg/rat) decreased the analgesic response to morphine when given i.t. or i.p. or in the periaqueductal gray matter. Pertussis toxin also inhibited the development of physical dependence as evidenced by inhibition of naloxone-precipitated teeth chattering, rearing, and grooming in the rat (Parolaro et al., 1990). In dependence studies, two morphine pellets (75 mg) were implanted 3 days after i.c.v. pretreatment with pertussis toxin (1 μg/rat). The withdrawal was precipitated with naloxone (2 mg/kg, i.p.) 72 h after the pellet implantation. These and earlier studies suggest that pertussis toxin-sensitive G-proteins are necessary for signal transduction in a series of events leading to the production of morphine-induced analgesia or dependence.

E. Drugs Modifying Immune Function

Attempts have been made to seek a relationship between immune function and morphine-induced tolerance and physical dependence. The time course of development of tolerance following initial drug exposure and the persistence of tolerance following abrupt removal of the drug was found to parallel the development and decline of immune reactions (Cochin and Kornetsky, 1964). Alterations in the humoral and cellular immune functions have been demonstrated in heroin addicts (Brown et al., 1974) as well as in morphine-tolerant and -dependent mice (Bhargava, 1990, 1991b; Bhargava et al., 1994; Bryant et al., 1988; Bryant and Roudebursh, 1990). Studies were undertaken to determine the effects of activation and inhibition of the immune system on morphine tolerance and physical dependence in mice. Immunization of mice by injection of 1 μg of 6-succinyl-morphine-bovine serum albumin increased the blood and brain levels of morphine and yet inhibited the development of tolerance and physical dependence on morphine. The development of tolerance and physical dependence was also inhibited by nonspecific immunosuppression using vincristine-cyclophosphamide injection and by total body irradiation of 500 rads of ^{60}Co γ-rays and specific immunosuppression by antithymocyte and antilymphocyte sera treatment (Meisheri and Isom, 1978).

F. Natural Products

1. Ginseng. Attempts have also been made to identify chemicals from the natural products that can be used to manage opioid addiction processes. One such product is the plant Panax ginseng. Administration i.p. of standardized Panax ginseng extract at a dose of 200 mg/kg produced analgesia (tail flick) and hypothermia, but when given in combination with morphine, ginseng antagonized the analgesic, hyperthermic, and cataleptic action of morphine in the rat. The analgesic and hypothermic responses to ginseng were not reversed by naltrexone, indicating a nonopioid receptor involvement in its actions (Ramarao and Bhargava, 1990b). Ginseng extract also inhibited the development of tolerance to analgesic and hyperthermic actions of morphine in the rat (Bhargava and Ramarao, 1991) and in mice (Kim et al., 1987). Because ginseng extract contains a number of saponins known as ginsenosides, the effect of individual ginsenosides on opioid tolerance and physical dependence needs to be determined.

IV. Drugs That Modify the Symptoms of Opioid Abstinence Syndrome

To develop pharmacotherapy for opioid addiction, several prerequisites for an ideal agent have been suggested (Kreek, 1992). The primary site of action or specific receptor at which the drug acts and the molecular, biochemical, and cellular events occurring in the drug addictive states, i.e., molecular mechanisms in the tolerance/dependence and abstinence syndrome should be clearly understood. Rational pharmacotherapy will probably not be possible unless such mechanisms are understood in both preclinical and clinical settings. Obviously, so far, such information is not available, and one has to depend on the observations made in the clinical settings. The desirable qualities of a opioid pharmacotherapeutic agent are that it should be orally effective with high bioavailability, have a long biological half-life generally >24 h, have minimal side effects during chronic administration, and have a high therapeutic index. In the following sections the effects of some opioid and nonopioid drugs on morphine abstinence syndrome in animals and humans will be described.

A. Exogenous Opioids

The use of clinical observation along with the existing preclinical knowledge led to the development of a chronic pharmacotherapy for the treatment of opioid (heroin) dependence by the use of the long-acting opioid, methadone (Dole et al., 1966). After chronic administration of morphine or heroin, tolerance to the euphoric and analgesic actions develops. Similarly, physical dependence also develops. Although the signs and symptoms of opioid abstinence syndrome are seen most prominently during the first 2 to 4 days after withdrawal (O'Brien et al., 1988), subtle signs and symptoms may be observed for 6 months or longer which may include depression and other abnormalities (Martin and Jasinsky, 1969). The heroin addict typically self administers the drug three to six times a day because it has relatively short duration

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of action to achieve euphoric feeling and to prevent narcotic withdrawal symptoms (Dole et al., 1966; Kreek, 1973). Methadone was found to be orally active with a half-life in the range of 24 to 36 h. It also reduces or eliminates drug craving and euphoria. Thus, it has been used as a once a day medication. A symptom that persisted in 50% of the subjects was increased sweating (Kreek, 1973, 1978). A much longer acting (3 to 4 days) drug than methadone is L-α-acetylmethadol (Young et al., 1979) which is also orally effective and has recently been approved for clinical use by the Food and Drug Administration.

B. Endogenous Opioids and Their Analogs

Chronic administration of opioids, particularly of morphine or heroin, has been shown to be associated with alterations in the levels of endogenous opioid peptides in the brain regions, cerebrospinal fluid, plasma or serum, and other peripheral tissues of animals and humans. In general, there is a decrease in the tissue levels of methionine-enkephalin, β-endorphin, and dynorphin (1–13) in morphine-tolerant and -abstinent rats (Bergstrom and Terenius, 1979; Bhargava et al., 1989b; Gudehithlu et al., 1991; Hollt et al., 1978; Przewloci et al., 1979; Rattan et al., 1992; Wesche et al., 1977), monkeys (Elsworth et al., 1986), and heroin-dependent human subjects (Clement-Jones et al., 1979; Ho et al., 1980; O'Brien et al., 1988; Volpe et al., 1986). Naloxone-precipitated withdrawal in morphine-dependent rats was shown to be associated with marked increases in enkephalin mRNA in the parvocellular paraventricular nucleus of the hypothalamus (Lightman and Young, 1987). In this study, morphine (8 mg/kg) was injected into rats twice daily on day 1, and 16 mg/kg was injected on day 2, which was then followed by delivering 60 mg/kg daily via osmotic minipumps. Naloxone (5 mg/kg, s.c.) was given on day 1 and on day 2, and osmotic minipumps delivering 20 mg/kg/day of naloxone were implanted into rats. The protocol used was rather difficult to understand.

On the other hand, rats made tolerant to morphine by s.c. implantation of pellets showed a significant decrease in striatal preproenkephalin mRNA that persisted during the period of withdrawal (Uhl et al., 1988). Levels of methionine-enkephalin were found to be normal at the end of the treatment but reduced after withdrawal of morphine.

Studies conducted in our laboratory showed differential changes in the levels of preproenkephalin mRNA in brain regions and spinal cord of morphine-tolerant and -abstinent rats. Rats were rendered tolerant/dependent by s.c. implantation of six morphine pellets (75 mg each) each containing 75 mg of morphine base, for a 7-day period. In morphine-tolerant rats, the levels of preproenkephalin mRNA were increased in cortex and spinal cord but were unchanged in corpus striatum, pons, and medulla. In morphine-abstinent rats, the levels of preproenkephalin mRNA were increased in corpus striatum but decreased in pons, medulla, and spinal cord (Gudehithlu and Bhargava, 1994). Because the levels of endogenous opioids as well as of their mRNA are altered in the CNS during abstinence from morphine, studies have, therefore, been undertaken to determine the effects of various opioid peptides and their analogs on the abstinence syndrome in morphine-dependent rodents and monkeys and heroin-dependent humans.

Chronic administration of the κ-opioid receptor agonist U-50,488H also modifies the levels of dynorphin A (1–13) (Bhargava et al., 1993), β-endorphin (Bhargava et al., 1994b), and methionine enkephalin (Tejwani et al., 1994) in discrete brain regions, spinal cord, pituitary, and peripheral tissues of the rat.

1. Natural and synthetic enkephalins. Soon after the discovery of the existence of opioid receptors in the mammalian brain, endogenous opioids were isolated. The major opioids are enkephalins, dynorphins, and β-endorphin. Studies in our laboratory and elsewhere have shown that methionine- and leucine-enkephalin, when injected i.c.v., inhibited the naloxone-precipitated withdrawal jumping response in morphine-dependent mice (Bhargava, 1977b, 1978b; Leybin et al., 1976). Further studies revealed that i.c.v. injections of two synthetic analogs of enkephalins, D-Ala^2,Met^5-enkephalinamide and D-Met^2-Pro^5-enkephalinamide, and morphine inhibited naloxone-precipitated withdrawal jumping and hypothermia as well as hypothermia seen during abrupt withdrawal in morphine-dependent mice. On a molar basis, D-Met^2-Pro^5-enkephalinamide and D-Ala^2-Met^5-enkephalinamide were 23 and 3 times, respectively, more potent than morphine in inhibiting morphine abstinence syndrome (Bhargava, 1980a). The effects of two enzyme-resistant analogs of enkephalin, namely, FK-33824 and metkephamid, administered either i.c.v. or s.c. to morphine-dependent rhesus monkeys have also been determined. Rhesus monkeys were maintained with morphine (3 mg/kg, s.c.) every 6 h for at least 90 days and then withdrawn for 12 to 16 h. Both compounds suppressed the abstinence syndrome in a dose-related fashion. FK-33824 was 100 times more potent in suppressing abstinence syndrome when given by the i.c.v. route than by the s.c. route, whereas metkephamid was 2000 times more potent when administered centrally in comparison to peripheral administration (Gmerek et al., 1983). Morphine was only 5 times more potent by the i.c.v. route than by s.c. injection. Morphine and FK-33824 administered i.c.v. suppressed withdrawal signs for 5 and 13 h, respectively (Gmerek et al., 1983). Administration of D-Ala^2,D-Leu^5 enkephalin (60 μg/kg) i.v. has been shown to significantly inhibit the withdrawal symptoms in heroin addicts for 1 h. However, it also produced many side effects, which included weakness of limbs, tightness of chest, precordial pain, headache, and warm sensation (Wen et al., 1984).

2. Natural and synthetic dynorphins. Dynorphin A(1–

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13) when administered i.c.v. has a weak analgesic action in the mouse tail-flick test (Friedman et al., 1981) and can inhibit both morphine- and β-endorphin-induced analgesia and suppress withdrawal jumping in morphine-dependent mice (Tulunay et al., 1981). Naloxone-precipitated withdrawal jumping has also been shown to be suppressed in morphine-dependent mice by dynorphin A (1–17), [D-Ala^2] dynorphin A (1–17), dynorphin A (1–10) amide, [Cys^5,Cys^{11}] dynorphin A (1–11) amide, dynorphin A (2–17), dynorphin A (2–8), dynorphin A (2–11), dynorphin A (2–14), and dynorphin A (3–13) when injected i.v. 5 min before the injection of naloxone (Takemori et al., 1993). The fact that dynorphin A (2–17) and its fragments were effective in inhibiting naloxone-precipitated withdrawal in morphine-dependent mice suggests that the actions of these peptides were not mediated via an interaction with the opioid receptors because these compounds do not bind to opioid receptors (Chavkin and Goldstein, 1981). Dynorphin A (1–13) injected i.v. or i.t. but not i.c.v. inhibited wet-dog shakes, yawns, abdominal stretches, and ptosis observed during abrupt withdrawal in morphine-dependent rats (Green and Lee, 1988). Similar effects of dynorphin A (1–13) have been observed in morphine-dependent rhesus monkeys (Aceto et al., 1982). Dynorphin A (1–13) injected i.v. (60 μg/kg) suppressed the withdrawal symptoms in heroin addicts which was associated with side effects such as a feeling of warmth, giddiness, dizziness, and precordial formication (Wen et al., 1984; Wen and Ho, 1982). Although dynorphin A (1–10) amide has been claimed to be a potent and a selective agonist of dynorphin A (1–13), the latter was found to be more potent than dynorphin A (1–10) amide in heroin addicts (Wen et al., 1984). It is important to note that i.t. administration of dynorphin A (1–13) has been reported to induce paralysis in the rat (Herman and Goldstein, 1985), and therefore, exhaustive toxicological data should be gathered before it can be recommended for clinical studies.

3. β-Endorphin. β-Endorphin administered i.c.v. in doses of 0.09 to 0.17 μg/mouse suppressed the withdrawal jumping induced by abrupt withdrawal of morphine from mice with implanted morphine pellets (Tseng et al., 1976). In this design, morphine pellets were removed from the mice, and 5 to 6 h later, the spontaneous jumpers and nonjumpers were given the test dose of β-endorphin. No other withdrawal sign was monitored. β-Endorphin (60 μg/kg, i.v.) also attenuated the withdrawal symptoms in heroin addicts for 45 min. Such an inhibition was associated with euphoria in some patients (Wen et al., 1984).

C. Inhibitors of Peptidases and Enkephalinases

The endogenous and exogenous enkephalins are degraded by enzymes termed enkephalinases A and B and aminopeptidases which are zinc-containing metallozymes (Schwartz, 1983; Roques et al., 1993). Inhibition of these enzymes presumably should increase the tissue levels of the enkephalins and other opioid peptides. The effects of several specific and nonspecific inhibitors of enkephalinases and peptidases on the opioid withdrawal syndrome have been studied. Administration of bacitracin and aprotinin i.c.v. decreased the behavioral withdrawal score, as well as epileptogenic expression in rats made dependent by increasing doses of morphine for 9 days and then precipitating the withdrawal by naloxone (Pinsky et al., 1982). Another enkephalinase inhibitor, phosphoramidon (50 to 200 μg, i.c.v.), suppressed naloxone-precipitated withdrawal jumping and wet-dog shakes, whereas forelimb shakes were potentiated in acute and chronic morphine-dependent mice (Dzoljic et al., 1986). The structures of various inhibitors of neutral endopeptidase 24.11 are provided in fig. 10. Injection of another enkephalinase inhibitor, thiorphan (40 μg), i.c.v. or into the periaqueductal gray matter inhibited the withdrawal precipitated by naloxone (4 mg/kg, i.p.) in rats made dependent on morphine by implantation of three 75-mg morphine pellets for 3 days (Haffmans and Dzoljic, 1987). Thiorphan was injected 10 min prior to the injection of naloxone. The symptoms that were suppressed included digging, head hiding, diarrhea, teeth chattering, wet-dog shakes, grooming, rearing, and paw tremor. In general, thiorphan injected into the periaqueductal gray matter was better than i.c.v. injection in inhibiting the symptoms of the abstinence syndrome (Haffmans and Dzoljic, 1987). Similar, effects have been

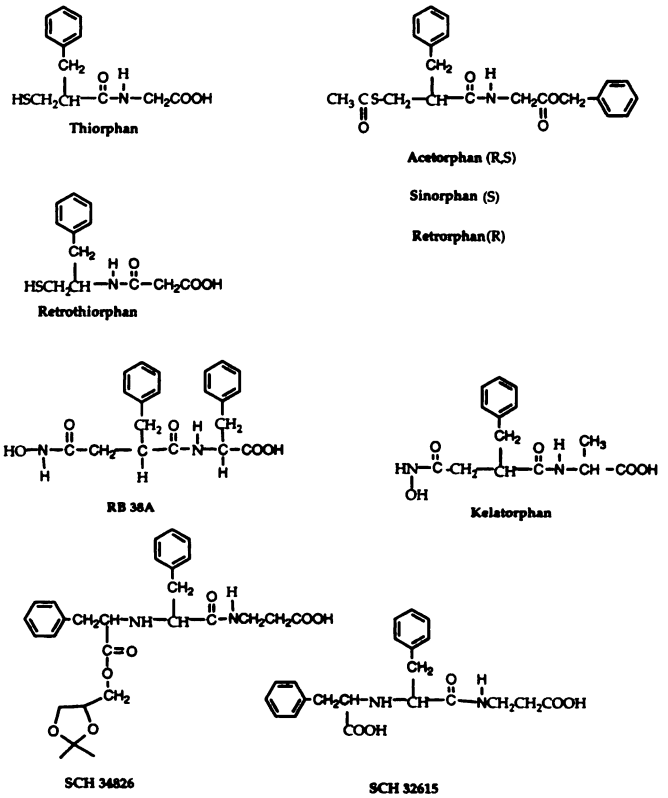

FIG. 10. Structures of neutral endopeptidase 24.11 (enkephalinase) inhibitors.

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observed with other mixed enkephalinase inhibitors, kelatorphan [(*R*)-3-(N-hydroxy-carboxamide-2-benzylpropanoyl)-L-alanine] and RB 38A [(*R*)-3-(N-hydroxy-carboxamido-2-benzyl propanoyl)-L-phenylalanine] (fig. 10), i.e., inhibition of jumping, chewing, and teeth chattering in naloxone-precipitated withdrawal in morphine-dependent rats. The body weight loss was unaffected by enkephalinase inhibitors (Maldonado et al., 1989). Finally, i.p. administration of orally effective enkephalinase inhibitors, acetorphan (2.5 to 20 mg/kg) and SCH 34826 (15 to 120 mg/kg) (Chipkin et al., 1988), decreased the severity of the naloxone-precipitated withdrawal syndrome in morphine-dependent mice and rats (Dzoljic et al., 1992).

D. Nonopioid Peptides

1. Thyrotropin-releasing hormone and analogs. TRH administered i.c.v. (1 to 50 μg) inhibited naloxone-precipitated withdrawal jumping in mice rendered dependent on morphine by pellet implantation. Similarly, the hypothermic response observed during abrupt or naloxone-precipitated withdrawal was inhibited by i.c.v. administration of TRH (Bhargava, 1980b). Such results are consistent with the observations of Morley et al. (1980), who demonstrated that during withdrawal the brain concentration of TRH decreases. Because TRH has a short half-life, the effects of its more stable analogs on morphine abstinence syndrome were determined. The naloxone-precipitated abstinence syndrome was also inhibited by cyclo (His-Pro), a metabolite of TRH, in morphine-dependent mice (Bhargava, 1981e). Effects similar to TRH were observed with two analogs, L-N-(2-oxo-piperidin-6-glycarbonyl)-L-histidyl-L-thiazolidine-4-carboxamide (MK-771) and γ-butyrolactone-4-carboxyl-histidyl-prolineamide (DN-1417) (Bhargava and Matwyshyn, 1985).

2. FMRF-NH_2-like peptides. When injected into the third ventricle of morphine-dependent rats, a low dose of NPFF precipitated the abstinence syndrome. On the other hand, intraventricular injection of IgG prepared from NPFF antiserum, prevented naloxone-precipitated abstinence syndrome in morphine-dependent rats (Malin et al., 1990b).

E. Drugs Related to Neurotransmitter and Second-Messenger Systems

A number of neurotransmitter systems have been implicated in playing a role in the expression of various symptoms of withdrawal from morphine. They include 5-HT, norepinephrine, dopamine, acetylcholine, adenosine, NMDA receptors, and some of their coupled second-messenger systems. Involvement of each of these systems will be described briefly.

1. Serotonin. The role of 5-HT receptors in morphine abstinence syndrome is not clear. Studies in this laboratory have demonstrated that in morphine-abstinent rats, 5-HT_1 receptors are up-regulated in certain brain regions, 5-HT_{1A} receptors are down-regulated in hypothalamus, and 5-HT_2 receptors appear to be unaffected (Gulati and Bhargava, 1988, 1989, 1990). The effect of drugs affecting the activity of 5-HT receptor systems on the expression of morphine abstinence syndrome has also been studied. When administered immediately before naloxone, two central 5-HT agonists, quipazine and meta-chlorophenylpiperazine, completely blocked naloxone-induced jumping in morphine-dependent rats (Samanin et al., 1980b). Mianserine, a 5-HT_2 receptor antagonist, was shown to suppress weight loss and hypothermia but not the increase in plasma corticosterone levels induced by naloxone-precipitated withdrawal in morphine-dependent rats (Neal and Sparber, 1986).

2. Norepinephrine. Considerable evidence suggests that opioid withdrawal syndrome may involve changes in central noradrenergic activity. Hypersensitivity to noradrenergic neurons has been established in the cerebral cortex of morphine-dependent rats (Llorens et al., 1978) as evidenced by increased B_{max} of [^{3}H]dihydroalprenolol binding and increased accumulation of cAMP in response to norepinephrine and isoproterenol. Similarly, increased activity of noradrenergic neurons has been seen in the locus coeruleus of morphine-dependent rats (Aghajanian, 1978) and primates (Redmond and Huang, 1982). Increased α_2-adrenergic receptors have been observed in rats treated chronically with morphine (Hamburg and Tallman, 1981; Smith et al., 1983). Hyperadrenergic activity in methadone-dependent human subjects given naltrexone has been evidenced by the increased concentration of plasma 3-methoxy-4-hydroxyphenylglycol, a metabolite of norepinephrine (Charney et al., 1984). Thus, both clinical and preclinical studies have provided evidence for the hyperadrenergic activity, and drugs have been used that modify adrenergic activity to treat the withdrawal symptoms in opioid-dependent subjects. Clonidine, an α_2-receptor agonist, injected i.p. (0.1 to 0.4 mg/kg) or i.c.v. (5 or 15 μg) inhibited naloxone-precipitated wet-dog shakes and escape attempts in morphine-dependent rats (Tseng et al., 1975) or nalorphine-induced shaking behavior in morphine-dependent rats (Vetulani and Bednarcyzk, 1977). Clonidine (6 to 100 μg/kg, s.c., or 0.1 to 10 μg, i.c.v.) also suppresses naloxone-induced (0.25 mg/kg, s.c.) withdrawal diarrhea (Schrier and Burks, 1981), conditioned behavior (disruption of operant behavior), and body weight loss (Sparber and Meyer, 1978) in morphine-dependent rats. Similar effects of clonidine and its analog lofexidin have been observed (Shearman et al., 1980). Clonidine and guanfacine inhibit both behavioral and autonomic components of morphine withdrawal in the rat (Buccafusco et al., 1984). Clonidine also eliminated objective and subjective symptoms of opioid withdrawal in 11 addicts. The patients had been addicted to opioid for 6 to 10 years and to methadone for 6 to 60 months (Gold et al., 1978, 1979).

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3. Dopamine

Although five types of dopamine receptors have been identified and cloned (O'Dowd, 1993), a majority of the studies of opioid tolerance/dependence or abstinence have involved D_1 and D_2 receptors (Kebabian and Calne, 1979). Dopamine D_1 receptors are linked to adenylate cyclase, whereas D_2 receptors are not. Although it has been known for several years that behavioral supersensitivity to dopamine agonists is observed in morphine- and β-endorphin-treated rodents, it was not clear which specific dopamine receptors were involved (Bhargava, 1981d, 1983a; Lal, 1975). Recent studies in our laboratory have shown that morphine-tolerant, -dependent, and -abstinent rats show differential changes in the central dopamine D_1 and D_2 receptors. In nonabstinent morphine-tolerant and -dependent rats, both D_1 and D_2 receptors are unaltered in brain regions and spinal cord when labeled with [^{3}H]SCH 23390 and [^{3}H]spiroperidol, respectively. In the abstinent rats, the binding (B_{max} value) of [^{3}H]SCH 23390 is increased in hypothalamus, corpus striatum, and spinal cord and decreased in amygdala, whereas the binding of [^{3}H]spiroperidol is unaffected in brain and spinal cord. However, the behavioral response to both D_1 and D_2 agonists, SKF 38393 and bromocryptine, respectively, are enhanced in morphine-abstinent rats (Bhargava and Gulati, 1990b; Reddy et al., 1993). Attempts have been made to modify the symptoms of abstinence by using drugs that act at the dopamine receptors. In general, dopamine agonists such as apomorphine enhance, whereas dopamine blockers such as haloperidol and butaclamol inhibit wet-dog shakes and aggressive behavior observed during withdrawal in morphine-dependent rats (Lal and Numan, 1976; Puri and Lal, 1973; Hynes et al., 1978). Haloperidol also inhibits withdrawal symptoms in human heroin addicts (Karkalas and Lal, 1973).

Although the cholinergic system interacts with many neurotransmitter systems, the cholinergic-dopaminergic link is well established. Thus, supersensitive dopamine receptors in opioid-dependent subjects may result in an enhanced inhibition of the cholinergic system. Thus, cholinergic agonists or haloperidol, a dopamine receptor antagonist, which also causes release of acetylcholine (Sethy and van Woert, 1974; Standler et al., 1973) should inhibit the abstinence syndrome as noted above.

4. Acetylcholine. Cholinergic drugs, both direct acting as well as indirect acting, such as physostigmine, an acetylcholinesterase inhibitor, suppress the naloxone-induced withdrawal jumping response in morphine-dependent mice (Bhargava and Way, 1972; Brase et al., 1974). Similarly, pilocarpine reduced the wet-dog shakes and aggression but enhanced diarrhea and weight loss in rats made dependent by multiple injections of morphine. Pretreatment with atropine and methyl-scopolamine blocked only the diarrhea induced by pilocarpine. The administration of atropine or dexetimide had no effect on any of the withdrawal symptoms (Hynes et al., 1976). There appears to be enhanced utilization of acetylcholine in the brain during morphine withdrawal (Domino and Wilson, 1973). Also, the brain concentration of acetylcholine is decreased during abstinence from morphine (Bhargava and Way, 1975; Domino and Wilson, 1975). However, the central cholinergic muscarinic receptors labeled with [^{3}H]quinuclidinylbenzilate are unaffected in morphine-tolerant or -abstinent rats (Das et al., 1984), indicating that the release of acetylcholine is modified during the abstinence process, although it is possible that other subtypes of muscarinic receptors as well as nicotinic receptors of the CNS may be affected in morphine-tolerant and -dependent subjects.

5. Benzodiazepine. The discovery of the high-affinity stereospecific benzodiazepine receptors in the CNS (Braestrup and Squires, 1977) has led to the clinical use of benzodiazepine receptor agonists and antagonists in many CNS-related disorders. Even before this discovery, benzodiazepines, which are anxiolytic agents, were used in the treatment of opioid abstinence syndrome. Thus, prazepam has been used to suppress symptoms of the opioid withdrawal syndrome in adult narcotic addicts (Sugerman et al., 1971), whereas diazepam has been used in neonates undergoing withdrawal (Nathenson et al., 1971). Similarly, chlordiazepoxide has been used in human narcotic addicts (Drummond et al., 1986, 1989). Administration of flunitrazepam, a benzodiazepine receptor agonist, decreases jumping and wet-dog shakes in morphine-dependent mice (Gibert-Rahola et al., 1988; Valverde et al., 1992) and rats (Baldino et al., 1979; Maldonado et al., 1991). Naloxone-precipitated withdrawal jumping and wet-dog shakes in morphine-dependent mice was increased by R015–4513, a partial inverse benzodiazepine receptor agonist, and flumazenil, a benzodiazepine receptor antagonist, but was decreased by flunitrazepam, a benzodiazepine receptor agonist or high doses of RO 16–6028, a partial agonist (Valverde et al., 1992).

6. Adenosine. The effects of the adenosine A_1 receptor agonist, PIA, the mixed adenosine A_1 and A_2 receptor agonist, adenosine-5′-ethylcarboxamide, and the adenosine A_2 receptor-selective agonist, 2-(phenylamino) adenosine (CV-1808) on naloxone-precipitated withdrawal have been studied in morphine-dependent rats (Dionyssopoulos et al., 1992). Morphine (125 mg/kg/day for 2 days) was injected s.c. into rats. Withdrawal was induced 24 h after the second dose. Adenosine analogs (30, 100, or 300 μg/kg, s.c.) were administered 20 min prior to naloxone (10 mg/kg, i.p.) injection. PIA and adenosine-5′-ethylcarboxamide produced a dose-related decrease in the total amount of fecal matter. CV-1808 had a similar effect but was not dose dependent. Behaviors such as paw shakes, body shakes, teeth chattering, and jumping were inhibited by PIA and adenosine-5′-ethylcarboxamide. The latter was more potent than PIA.

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CV-1808 caused a reduction in only the incidence of teeth chattering. Locomotor activity was reduced by all drugs (Dionyssopoulos et al., 1992). Finally, treatment of rats with morphine by using multiple injections has been shown to down-regulate adenosine A_1 receptors in the spinal cord but not in cortex (Tao and Liu, 1992).

7. Calcium channel blockers. Considerable evidence suggests that morphine exhibits its analgesic activity at least in part through the inhibition of calcium influx, thereby reducing the release of transmitters. Morphine reduces the calcium content in the brain synaptosomes (Cardenas and Ross, 1976; Harris et al., 1977; Yamamoto et al., 1978). Calcium also antagonizes the analgesic action of morphine (Kakunaga et al., 1966). Calcium channel blockers appear to produce analgesic action (Del Pozo et al., 1987). Using the acetic acid writhing test, Ohnishi et al. (1988) demonstrated that the analgesic effect of nifedipine, a calcium channel blocker, was decreased in morphine-tolerant mice. Thus, calcium influx may be one of the mechanisms of the analgesic action of morphine, and chronic administration of morphine produces an increase of calcium entry. Increased density of [^{3}H]nitrendipine (a calcium channel blocker) binding sites has been observed in the mouse and rat brain (Ramkumar and El-Fakahany, 1984, 1988), rat striatum (Saito et al., 1985), and rat hippocampus (Ohnishi et al., 1989) when the animals were treated chronically with morphine, suggesting an increase in the number of calcium channels.

Calcium channel blockers (fig. 11) appear to inhibit, whereas calcium channel stimulants augment, the withdrawal precipitated by naloxone in rat ileum (Barrios and Baeyens, 1988). In morphine-dependent rats, i.p. administration of verapamil and flunarizine prevented diarrhea and weight loss but not jumping observed during withdrawal. Verapamil at 40 mg/kg reduced the incidence of ptosis. Administration of verapamil (160 μg/kg, i.c.v.) reduced the body weight loss and jumping response without modifying diarrhea or ptosis. Thus, both central and peripheral mechanisms are important in the inhibition of morphine abstinence syndrome by calcium channel blockers (Baeyens et al., 1987). Similar effects have been demonstrated with the isomers of diltiazem, *d-cis* being more potent than *l-cis* isomer in inhibiting naloxone-precipitated withdrawal in morphine-dependent mice and in morphine-dependent rat ileum (Caro et al., 1988). Verapamil, diltiazem, and nicardipine also decreased forepaw tremor, body weight loss, and jumping in mice acutely dependent on morphine. On the other hand, the calcium channel agonist Bay K 8644 increased forepaw tremor and body weight loss (Barrios and Baeyens, 1991). In another study, verapamil and nimodipine were reported to inhibit naloxone-precipitated withdrawal symptoms in morphine-dependent rats. These effects were produced by an action independent of opioid receptors because neither agent displaced [^{3}H]naloxone from its binding sites. Nimodipine pretreatment also antagonized the decreases in norepinephrine content and increases in 3-methoxy-4-hydroxyphenylglycol levels in the cortex, brainstem, and hippocampus induced by the abstinence syndrome (Bongianni et al., 1986). Additionally, the agents that modify Ca^{2+} fluxes, such as lanthanum and copper, when injected i.c.v. reduced the signs of morphine abstinence (Bhargava, 1978d; Harris et al., 1975).

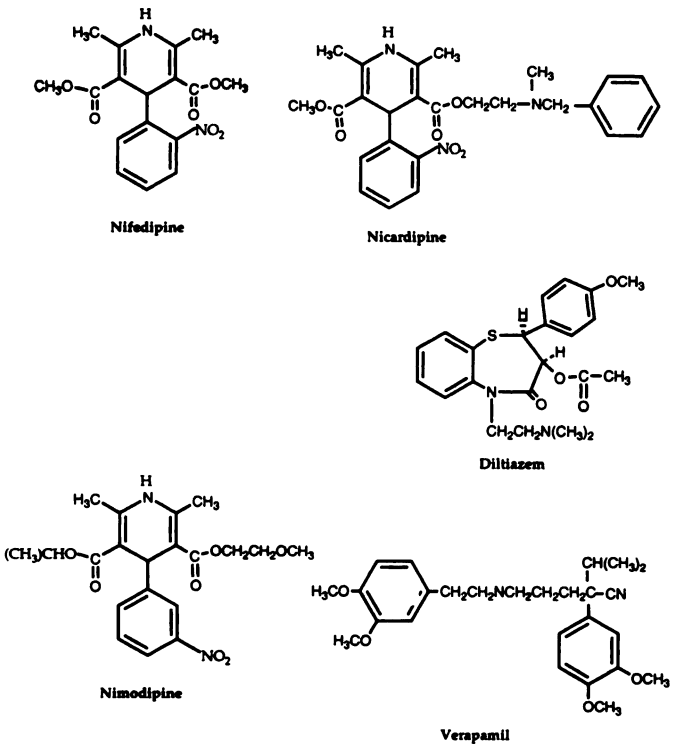

FIG. 11. Structures of calcium channel blockers.

8. Excitatory amino acid antagonists. A possible interaction between excitatory amino acids and opioids was discussed earlier. Attempts have also been made to study the effects of NMDA receptor antagonists on the naloxone-precipitated abstinence syndrome. In mice rendered dependent on morphine by pellet implantation, MK-801 (0.1 mg/kg, i.p.) did not alter the jumping response, but a 1.0-mg/kg dose of MK-801 significantly reduced the jumping response precipitated with 0.05 mg/kg of naloxone. In mice made dependent by multiple injections of morphine for 9 days, MK-801 (0.17 mg/kg, i.p.) abolished jumping behavior induced by naloxone (1 mg/kg, i.p.). On the other hand, 0.054 mg/kg of MK-801 increased jumping behavior (Marquis et al., 1991). Because of this complex interaction, studies were undertaken in this laboratory to determine the effect of MK-801 on naltrexone-precipitated withdrawal in mice made dependent by morphine (75 mg) pellet implantation. Injection of MK-801 (0.03, 0.1, and 0.3 mg/kg, i.p.) given 30 min before naltrexone (50 μg/kg, s.c.) did not modify stereotyped jumping behavior, body weight loss, body

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temperature, or formation of fecal boli (Matwyshyn et al., 1993; Thorat et al., 1994).

The effects of MK-801, a noncompetitive receptor antagonist that acts by blocking the ion channel (Wong et al., 1988), and LY 274614, a competitive NMDA receptor antagonist that acts through an action at the glutamate recognition site (Ornstein et al., 1990), on morphine abstinence syndrome have also been determined in the rat (Rasmussen et al., 1991). Rats were made dependent on morphine by implanting two morphine pellets daily for 2 days. The pellets were removed 48 h after the last set of pellets was implanted. After an additional 2- to 3-h period, rats were treated with naltrexone. MK-801 (0.1 and 1.0 mg/kg) pretreatment significantly suppressed teeth chattering, erections, ptosis, chewing action, wet-dog shakes, weight loss, lacrimation, and diarrhea. The symptoms that were unaffected included writhes, jumping, and salivation. In fact, 0.1 mg/kg of MK-801 increased the number of wet-dog shakes. Similarly, LY 274614 (50 and 100 mg/kg) suppressed the same behaviors as did MK-801 but did not affect the symptoms such as writhes, jumps, wet-dog shakes, salivation, and lacrimation. MK-801 pretreatment was associated with PCP-like behaviors which included head weaving, locomotion, and falling. On the other hand, pretreatment with LY 274614 produced no PCP-like behaviors but produced a mild to marked degree of sedation (Rasmussen et al., 1991). Thus, studies in both mice and rats indicate that NMDA receptor antagonists inhibit many symptoms of the antagonist-induced abstinence syndrome but do not affect stereotyped jumping response. Hence, responses other than jumping should be evaluated when studying the action of any agent on the opioid abstinence syndrome. Finally, studies in our laboratory have demonstrated that in the presence of glycine and glutamic acid, the binding of [^{3}H]MK-801 is decreased in several brain regions in morphine-abstinent rats, which suggest that the central NMDA receptors are modified during chronic treatment of rats with morphine (Gudehithlu et al., 1993).

9. Nitric oxide synthase inhibitors. Recent studies in our laboratory indicated that NOS inhibitors such as L-NMMA (0.02 to 4 mg/kg, i.p.) injected 15 min prior to naltrexone (50 μg/kg, s.c.) injection inhibited the stereotyped jumping response but did not affect other withdrawal signs in morphine-dependent mice (Matwyshyn et al., 1993; Thorat et al., 1994). Similar effects have been observed with N^G-nitro-L-arginine, another inhibitor of NOS on morphine abstinence syndrome in mice (Kolesnikov et al., 1993). The effects of several NOS inhibitors, namely, N^G-nitro-L-arginine methyl ester, L-N^G-nitro-L-arginine, and L-NMMA were determined on naloxone-precipitated withdrawal in morphine-dependent mice. L-N^G-Nitro-L-arginine methyl ester (30 to 200 mg/kg) and L-N^G-nitro-L-arginine (7.5 to 50 mg/kg) administered i.p. induced a significant decrease of naloxone (4 mg/kg, i.p.) precipitated withdrawal jumping and diarrhea (Cappendijk et al., 1993). These investigators, however, did not observe any effect with L-NMMA (3.5 to 100 mg/kg) on withdrawal signs, which is in contrast with other studies (Matwyshyn et al., 1993; Thorat et al., 1994). In the latter studies L-NMMA was injected 15 min prior to naloxone, whereas in the studies of Cappendijk et al. (1993) it was given 30 min before naloxone injection. In addition, dependence was induced by implanting a 25-mg morphine pellet, and the dose of naloxone was 4 mg/kg (Cappendijk et al., 1993). In contrast, Thorat et al. (1994) used a 75-mg morphine pellet and induced withdrawal with 50 μg/kg of naltrexone. L-N^G-Nitro-L-arginine (7.5 mg/kg) and its methyl ester (60 mg/kg) given i.p. 1 h before naloxone injection reduced wet-dog shakes and weight loss but increased teeth chattering in morphine-dependent rats (Kimes et al., 1993). It appears, therefore, that NOS inhibitors may be of potential value in managing opioid abstinence syndrome.

F. Natural Products

1. Marijuana constituents. The chemical constituents of marijuana (*Cannabis sativa*) known as cannabinoids have been shown to modify the symptoms of antagonist-induced withdrawal in morphine-dependent rodents. Several studies have shown that morphine and Δ^9-THC share many pharmacological properties, such as analgesia, hypothermia, respiratory depression, locomotor depression, tolerance development, etc., even though the mechanisms of action of these two compounds are quite different. More recently, a bidirectional cross-tolerance between morphine and Δ^9-THC has been demonstrated in mice (Thorat and Bhargava, 1994). Therefore, it is not surprising to see the modification of symptoms of antagonist-induced withdrawal by cannabinoids in morphine-dependent rodents. The withdrawal-induced wet-dog shakes and defecation responses were inhibited by Δ^9-THC in morphine-dependent rats (Hine et al., 1975). In mice rendered dependent on morphine by pellet implantation, i.p. administration of Δ^9-THC (2.5 to 10 mg/kg) 30 min before the s.c. injection of naloxone inhibited the stereotyped jumping response (as evidenced by the increases in the ED$_{50}$ values of naloxone for precipitating the response), defecation, and rearing behavior (Bhargava, 1976a). Δ^8-THC, 11-hydroxy-Δ^8-THC, cannabidiol, and cannabinol also inhibited the responses. Δ^9-THC was the most potent agent; cannabinol was the least potent (Bhargava, 1976b). Further studies of the time course of the effects of cannabinoids revealed that 10 mg/kg of Δ^9-THC was effective for 24 h in inhibiting the jumping response, whereas Δ^8-THC and 11-hydroxy-Δ^8-THC were effective for only 2 h. This inhibition in naloxone-precipitated jumping response by cannabinoids appeared to be specific, because the vertical jumping syndrome induced by coadministration of amphetamine

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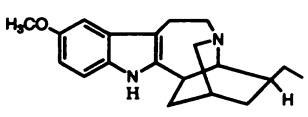
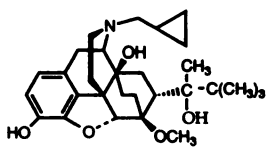
and levodopa was not affected by cannabinoids (Bhargava, 1978c).

2. Ibogaine. Ibogaine (fig. 12), an indole alkaloid isolated from the root bark of the African shrub *Tabernanthe iboga*, has been claimed to "interrupt the physiological and psychological aspects of the opioid withdrawal syndrome" and suppress the multiple symptoms and physical discomfort of narcotic withdrawal (Lotsof, 1985). A single oral dose of ibogaine or its salts in dosages of 6 to 19 mg/kg was claimed to be effective for 6 months in patients undergoing opioid withdrawal syndrome. These studies triggered several investigations in morphine-dependent animals to either substantiate or repudiate this claim. Dzoljic et al. (1988) reported that i.c.v. administration of ibogaine (4 to 16 μg/rat) attenuated rearing, digging, head hiding, chewing, teeth chattering, writhing, jumping, and salivation induced by naloxone (5 mg/kg, i.p.) in morphine-dependent rats, but the frequency of wet-dog shakes, head shakes, stretching, grooming, scratching, vocalization on touch, ptosis, diarrhea, urination, rhinorrhea, paw tremor, and ejaculation was not affected. On the other hand, penile licking was significantly increased. Sharpe and Jaffe (1990) found that s.c. administration of ibogaine did not attenuate naloxone-precipitated withdrawal signs in morphine-dependent rats except for a decrease in the grooming behavior. In morphine-dependent monkeys, Aceto et al. (1990) reported that s.c. administration of ibogaine partially suppressed withdrawal signs. In a more recent study, Glick et al. (1992) reported that i.p. administration of ibogaine 30 min before naltrexone challenge reduced wet-dog shakes, grooming, teeth chattering, and diarrhea. However, weight loss, burying, and flinching were unaffected in morphine-dependent rats. These differences may possibly be due to the route of administration, doses of ibogaine, the interval between administration of ibogaine and the antagonist, and the method used to induce the dependence on morphine. Ibogaine induces head and body tremors, the duration of which depends on the dose. This tremorogenic behavior could interfere with the observations and interpretations of the results on morphine withdrawal syndrome. Glick et al. (1992) reported that the tremors subside within 2 to 3 h and are absent 4 h after the administration of ibogaine. When given 4 h before naltrexone injection, ibogaine still was found to be effective in ameliorating the withdrawal signs, suggesting an independence from its tremor-producing action.



Ibogaine



Buprenorphine

FIG. 12. Structures of drugs affecting opiod self-administration.

The mechanism by which ibogaine suppresses some opioid withdrawal signs is not known. Ibogaine appears to have a low affinity for κ-opioid-binding sites with a K_i value of 2 μM (Deecher et al., 1992). Ibogaine has complex interaction with neurotransmitter systems, including noradrenergic, cholinergic, and 5-HT (Dhahir, 1971). Ibogaine appears to activate 5-HT receptors, and 5-HT_2 receptor antagonists, such as methysergide, reduce the hypotensive action of ibogaine (Dhahir, 1971). Further studies are obviously warranted to clarify the mechanism of action of ibogaine in opioid withdrawal syndrome.

Given the fact that a single oral dose of ibogaine was effective for 6 months in controlling opioid withdrawal symptoms, it is possible that the effect may be due to a metabolite with a long biological half-life. Such studies are obviously warranted.

G. Immunomodulators

In recent years, much interest has developed in the field of neuroimmunological and psychoneuroimmunological aspects of opioids. Substantial evidence exists to suggest that the nervous system can influence the immune function and vice versa. It is also known that chronic morphine treatment not only influences the CNS but also the immune function (Bhargava, 1990, 1991b; Bhargava et al., 1994d).

1. Interferon. Interferon, a naturally occurring protein, stimulates natural killer cell activity (Heberman et al., 1979; Huddlestone et al. 1979), decreases the number of circulating B-lymphocytes (Rasmussen et al., 1980), and inhibits T-cell proliferative responses (Weinstein et al., 1977; Mittelman et al., 1983). Morphine has been shown to decrease the circulating levels of interferon (Vilcek et al., 1968; Hung et al., 1973). Injection i.p. of recombinant leukocyte A interferon (150 units/g) 1 h prior to naloxone (1 mg/kg) injection to rats made dependent on morphine by implantation of a 75-mg morphine pellet reduced or eliminated wet-dog shakes, teeth chattering, fecal boli formation, hyperactivity, exploring behavior, and diarrhea (Dafny, 1983). Although the mechanism by which interferon inhibits morphine abstinence syndrome is not known, it has structural similarity to adrenocorticotropic $hormone_{1-13}$ and β-endorphin (Blalock and Smith, 1980). In addition, human peripheral lymphocytes are capable of producing adrenocorticotropic hormone and endorphin-like substances, the former being strongly associated with interferon (Smith and Blalock, 1981). Finally, human leukocyte interferon has been shown to bind to opioid receptors in vitro (Blalock and Smith, 1981).

2. Cyclosporine. Effects similar to interferon have been demonstrated for cyclosporine, a fungal polypeptide and an immunosuppressive agent (Dafny et al., 1985). Cyclosporine produces its action on helper T- and B-lymphocytes. Effects similar to interferon have been observed with cyclosporine (15 mg/kg, i.p.) injected 2 h prior to naloxone (1 mg/kg, i.p.) in morphine-dependent rats (Dafny et al., 1985). The results of the studies with

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immunomodulators suggest that further studies in this area may yield therapeutically useful drugs.

H. Miscellaneous Agents

1. Ethanol. Ethanol (0.5 to 2.0 g/kg) has been reported to suppress diarrhea, wet-dog shakes, and jumping response and to enhance hypothermia observed following naloxone administration to rats made dependent by a single morphine pellet implantation for 3 days (Ho et al., 1979). The effect of ethanol on withdrawal-induced diarrhea was nonspecific because ethanol suppressed diarrhea induced by castor oil as well (Ho et al., 1979).

2. Calcium. Acute and chronic administration of morphine produces a naloxone-sensitive decrease in regional brain calcium stores that is dose and time dependent (Cardenas and Ross, 1975, 1976; Ross, 1977). Injection of calcium (45 mg/kg, i.p.) 1 h prior to naloxone (5 mg/kg) challenge in rats made dependent on morphine by implantation of a single morphine (75 mg) pellet inhibited wet-dog shakes, fecal boli formation, diarrhea, and ptosis and prevented the loss of calcium in brain induced by morphine treatment (Sanghvi and Gershon, 1977). Thus, elevation of calcium in the brain alleviates the signs of naloxone-precipitated abstinence syndrome in morphine-dependent rats. It was suggested that this action of calcium may be related to the effect of morphine on adenylate cyclase activity (Sanghvi and Gershon, 1977).

3. Calcitonin. Injection i.m. of eel calcitonin ([Asu^{1-7}] eel calcitonin), an analog of natural eel calcitonin, (10 IU/kg) 30 min prior to naloxone (2.5 mg/kg, s.c.) injection did not modify the withdrawal symptoms in rats made dependent on morphine by multiple injections of increasing doses of morphine for 14 days (Clementi et al., 1989). The effects of routes of administration, other than i. m., of calcitonin or its analogs on morphine abstinence syndrome are not known. In one study, elevated levels of calcitonin in serum of heroin addicts were found to be lowered by methadone or clonidine detoxification treatment (Tagliaro et al., 1985). Further studies using varying doses and routes of administration are necessary.

V. Drugs Affecting Self-Administration of Opioids

Considerable evidence suggests that opioids activate the mesolimbic systems, particularly the ventral tegmental area and nucleus accumbens, where they increase dopaminergic impulse flow and elevate extracellular levels of dopamine (Di Chiara and Imperato, 1988). Rats have been shown to self-administer (lever press) μ- (morphine) or δ- (enkephalins) but not κ- (ethylketocyclazocine or U-50,488H) opioid injections into ventral tegmental area or nucleus accumbens (Koob and Bloom, 1988). Additionally, morphine self-administration has been reported to be modified by lesioning caudate nucleus in the rat (Glick et al., 1975). Attempts have been made to study the effects of drugs that could decrease craving and self-administration of heroin. The effects of major drugs, buprenorphine, ibogaine, and oxytocin and vasopressin fragments on morphine or heroin self-administration will be described briefly.

A. Buprenorphine

Buprenorphine (fig. 12) chemically related to cyclazocine and naltrexone is a partial opioid receptor agonist-antagonist-type analgesic with low dependence liability. The drug is remarkably safe and devoid of toxicity because it has a biphasic dose-response curve that puts a ceiling on its agonist actions (Lewis et at., 1983). Several studies have been undertaken to determine the effects of buprenorphine in heroin addicts. The sum of these studies demonstrated that buprenorphine is accepted by heroin addicts, suppresses their use of heroin, is effective for detoxification, and can block the effects of opioids (Bickel et al., 1988a,b; Fudala et al., 1990; Jasinski et al., 1978; Johnson et al., 1989; Kosten and Kleber, 1988; Mello et al., 1982; Reisinger, 1985). Heroin-dependent subjects who refused to accept methadone maintenance treatment and failed to demonstrate a positive response by naltrexone-induced negative reinforcement procedure or to join a residential therapeutic community found buprenorphine an acceptable modality (Resnick et al., 1991). In a more recent study, 85 heroin addicts who were unwilling to receive methadone treatment received buprenorphine sublingually in a dose range of 1.5 to 80 mg/day. Burprenorphine was found to reduce heroin craving and use (Resnick et al., 1992). Gradual dose reduction of buprenorphine led to the development of abstinence symptoms, which included "low energy," restlessness, insomnia, anorexia, muscle pain, diarrhea, and yawning. In addition, it also produced a concomitant drug-seeking behavior in the heroin addicts (Resnick et al., 1992). Thus, the sublingual use of buprenorphine may be a preferred modality compared to the deleterious consequences of continued i.v. use of heroin by the subjects because the latter is associated with problems of transmission of human immunodeficiency virus and development of the autoimmune deficiency syndrome. These results suggest that buprenorphine can be added to the armamentarium of drugs for the treatment of addicts to reduce craving and self-administration of morphine or heroin.

B. Ibogaine

Ibogaine has been shown to potentiate the analgesic action of morphine (Schneider and McArthur, 1956). In addition to suppressing some symptoms of antagonist-precipitated withdrawal in morphine-dependent animals, ibogaine (fig. 12) has also been shown to suppress i.v. self-administration of morphine in rats. This effect was dose dependent (2.5 to 80 mg/kg) during the first hour of treatment and persisted for several days or weeks after a single injection. As noted earlier, ibogaine causes

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tremors which subside in less than 4 h after its administration. Because the decrease in morphine self-administration persisted for longer than its effect on tremors, the two effects could be dissociated (Glick et al., 1991). Such effects would be consistent with the claims of the efficacy of ibogaine in treating opioid addiction (Lotsof, 1985). It must be noted, however, that the effects of ibogaine were not specific to opioids but were equally effective for stimulant drugs such as cocaine or amphetamines (Lotsof, 1986).

Attempts have also been made to examine the mechanisms by which ibogaine decreases self-administration of morphine in rats. Self-administrative behavior for various drugs of abuse appears to involve dopaminergic systems in the mesolimbic and mesocortical areas of the brain (Di Chiara and Imperato, 1988; Wise and Bozarth, 1982). Most drugs of abuse increase the extracellular concentration of dopamine in the nucleus accumbens and to a lesser extent in the striatum (Di Chiara and Imperato, 1988); however, the mechanisms by which each drug increases dopamine levels is quite different. Ibogaine (40 mg/kg, i.p.) was shown to decrease dopamine levels in the striatum, increase them in the prefrontal cortex, and had no significant effect in the nucleus accumbens. However, when injected 19 h prior to a morphine injection (5 mg/kg, i.p.), ibogaine (40 mg/kg, i.p.) prevented the increase in dopamine levels in all three regions (Maissonneuve et al., 1991). Although there may be other mechanisms involved, interference with the dopaminergic systems involved in reward or reinforcement may be one of the mechanisms by which ibogaine interferes with i.v. self-administration of morphine.

C. Oxytocin and Vasopressin Fragments

Our earlier studies had demonstrated that oxytocin, vasopressin, and some of their analogs were capable of inhibiting morphine tolerance and physical dependence (Bhargava, 1986). The effects of several behaviorally active fragments of oxytocin were determined on i.v. self-administration of heroin in the rat. Injections s.c. of oxytocin$_{1-9}$, desglycinamide oxytocin (oxytocin$_{1-8}$), and [pGlu^4,Cyt^6] oxytocin$_{4-8}$ (oxytocin$_{4-8}$) were found to decrease the amount of heroin self-injected. On the other hand, the COOH-terminal tripeptide of oxytocin, MIF, and desglycinamide^9-[Arg]^8-vasopressin were ineffective in decreasing self-administration of heroin in the rat (Kovacs and van Ree, 1985). The decrease in self-administration of heroin by the active peptides was associated with a decrease in tolerance development. The same authors, however, reported earlier that MIF facilitated morphine tolerance but decreased self-administration of morphine (van Ree and de Wied, 1976). The reasons for the inconsistencies in the two studies are not apparent at this time.

VI. Conclusions and Future Prospects

The appearance of opioid addiction following chronic administration of opioids puts serious limitations on their use for the relief of pain of moderate to severe intensity. In addition to this problem for the legitimate use in clinics, opioids abuse, particularly of morphine and heroin, has become a worldwide phenomenon. With increasing abuse of opioids and other drugs, the sharing of needles has proliferated the spread of human immunodeficiency virus and autoimmune disease.

Concerted efforts are required from various disciplines, such as behavioral, biochemical, and molecular pharmacology and immunology, to further elucidate the central and peripheral mechanisms in pharmacological, endocrinological, and immunological actions of opioids.

In spite of considerable efforts devoted to understanding the mechanisms involved in the production of opioid-induced tolerance, physical dependence, abstinence syndrome, and self-administrative behavior, they are still poorly understood. Nevertheless, several agents have been shown to modify these processes. Although μ-opioid receptor antagonists block tolerance/dependence on morphine, they also antagonize the analgesic response to morphine and, therefore, may not be useful clinically in inhibiting the morphine tolerance/dependence process. On the other hand, δ-selective opioid receptor antagonists do not modify morphine analgesia but block the morphine tolerance/dependence process and, therefore, may have therapeutic potential. However, it must be noted that chronic administration of δ-opioid antagonists, such as naltrindole, produce immunosuppression (Arakawa et al., 1993) and may add to the immunosuppression induced by opioid addiction processes. Further studies may help us understand the underlying mechanisms of these interactions.

Neuropeptides such as TRH, MIF, CCK, and their analogs, which may act as endogenous opioid antagonists, produce actions similar to exogenous opioid antagonists, although their mechanisms of actions may be quite different. Cyclo (Leu-Gly), an orally active analog of MIF, inhibits tolerance and physical dependence on morphine, and further studies are necessary to delineate its mechanism of action. CCK-B receptor antagonists enhance morphine analgesia and inhibit tolerance to morphine without affecting the development of physical dependence (Panerai et al., 1987).

NMDA receptor antagonists, such as MK-801, inhibits the development of tolerance to the analgesic action of morphine and U-50,488H selectively but are quite toxic especially when combined with μ- or κ-opioid receptor agonists. On the other hand, competitive NMDA receptor antagonists such as LY 274,614 also inhibit tolerance to opioids but are less toxic. NOS inhibitors are the newest drugs on the scene, which inhibit both tolerance and physical dependence development on opioids. The

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side effects, such as an increase in blood pressure, must be evaluated further.

The opioid abstinence syndrome is modified by a variety of agents. Orally acting agents with long duration of action such as methadone and L-α-acetylmethadol are the drugs of choice for substitution therapy. Because, in general, in morphine- or heroin-addicted subjects the levels of endogenous opioids in the CNS decrease, which leads to the appearance of symptoms of the withdrawal syndrome, replenishing the stores of endogenous opioids suppresses the symptoms. In this regard, preclinical and clinical studies suggest that dynorphin analogs and related compounds may be useful. However, they will not be effective orally. Additionally, the toxicity of dynorphin (analogs) must be evaluated carefully. On the other hand, orally effective enkephalinase inhibitors, which apparently increase the levels of endogenous opioids, may prove to be good therapeutic agents. Drugs that inhibit noradrenergic and dopaminergic activity (clonidine and antipsychotic agents) and/or increase central cholinergic activity may be useful for management of opioid withdrawal syndrome, but they possess their own side effects. Similarly, NMDA receptor antagonists, NOS inhibitors, and benzodiazepine anxiolytic may also be useful adjuncts. Further exploration of the use of immunomodulators and calcium channel blockers in the management of opioid abstinence syndrome is necessary.

Self-administrative behavior is an important component of opioid addiction processes. Buprenorphine appears to decrease the craving and self-administration of heroin. Several studies have shown positive results with buprenorphine in heroin addicts for whom methadone or related compounds and opioid antagonists such as naltrexone are not acceptable choices. Buprenorphine will probably be approved by the Food and Drug Administration soon. Another compound of interest is ibogaine which has been shown to decrease self-administration of morphine in animals as well as in human addicts. Obviously, further studies of ibogaine and its analogs on self-administration of opioids are necessary. In addition, much needs to be learned about the toxicity of ibogaine and its analogs.

Because a variety of agents with different chemical structures and biochemical mechanisms affect opioid addiction processes, it is possible that the mechanism involved in their actions may be related to second-messenger systems. Understanding these mechanisms will certainly help in designing drugs that can inhibit opioid tolerance, physical dependence, abstinence syndrome, and self-administrative behavior.

Neuropeptides such as TRH, MIF, and cyclo (Leu-Gly) appear to produce similar results, although their mechanisms of action may be quite different. Cyclo (Leu-Gly) produces its action when administered orally, and therefore further studies of this peptide are warranted. CCK-B receptor antagonists enhance morphine analgesia and block tolerance to morphine but have no effect on the development of dependence on morphine (Panerai et al., 1987). Recent studies that have shown that ginseng can inhibit the development of morphine tolerance and physical dependence suggest that antiopioid substances can be derived from natural products. Similarly, ibogaine has been shown to inhibit the symptoms of morphine abstinence syndrome and self-administration of heroin. Exploration of agents from natural products such as ginseng and the root bark of the African shrub *T. iboga* may also prove to be fruitful.

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REFERENCES

ABDELHAMID, E. E., SULTANA, M., PORTOGHESE, P. S., AND TAKEMORI, A. E.: Selective blockage of δ opioid receptors prevents the development of morphine tolerance and dependence in mice. J. Pharmacol. Exp. Ther. **258:** 299–303, 1991.

ABDELHAMID, E. E., AND TAKEMORI, A. E.: Characteristics of μ and δ opioid binding sites in striatal slices of morphine tolerant and dependent mice. Eur. J. Pharmacol. **198:** 157–163, 1991.

ACETO, M. D., BOWMAN, E. R., AND HARRIS, L. S.: Dependence studies of new compounds in the rhesus monkey, rat and mouse. NIDA Res. Monogr. **95:** 578–631, 1990.

ACETO, M. D., DEWEY, W. L., CHANG, J. K., AND LEE, N. M.: Dynorphin-(1–13): effects in non-tolerant and morphine-dependent rhesus monkeys. Eur. J. Pharmacol. **83:** 139–142, 1982.

ACETO, M. D., DEWEY, W. L., PORTOGHESE, P. S., AND TAKEMORI, A. E.: Effect of β-funaltrexamine (β-FNA) on morphine dependence in rats and monkeys. Eur. J. Pharmacol. **123:** 387–393, 1986.

AGHAJANIAN, G. K.: Tolerance of locus coeruleus neurons to morphine and suppression of withdrawal responses by clonidine. Nature **276:** 186–188, 1978.

AHLIJANIAN, M. K., AND TAKEMORI, A. E.: Effects of (−)-N^6-(R-phenylisopropyl) adenosine (PIA) and caffeine on nociception and morphine-induced analgesia, tolerance and dependence in mice. Eur. J. Pharmacol. **112:** 171–179, 1985.

ANTKIEWICZ-MICHALUK, L., MICHALUK, J., ROMANSKA, I., AND VETULANI, J.: Reduction of morphine dependence and potentiation of analgesia by chronic co-administration of nifedipine. Psychopharmacology **111:** 457–464, 1993.

ARAKAWA, K., AKAMI, T., OKAMOTO, M., AKIOKA, K., NAKAI, I., OKA, T., AND NAGASE, H.: Immunosuppression by delta opioid receptor antagonist. Transplant. Proc. **25:** 738–740, 1993.

BADAWY, A. A. B., EVANS, C. M., AND EVANS, M.: Production of tolerance and physical dependence in the rat by simple administration of morphine in drinking water. Br. J. Pharmacol. **75:** 485–491, 1982.

BAEYENS, J. M., ESPOSITO, E., OSSOWSKA, G., AND SAMANIN, R.: Effects of peripheral and central administration of calcium channel blockers on the naloxone-precipitated abstinence syndrome in morphine-dependent rats. Eur. J. Pharmacol. **137:** 9–13, 1987.

BALDINO, F., COWAN, A., GELLER, E. B., AND ADLER, M. W.: Effects of antipsychotic and antianxiety drugs on morphine abstinence syndrome in rats. J. Pharmacol. Exp. Ther. **208:** 63–66, 1979.

BARRIOS, M., AND BAEYENS, J. M.: Differential effects of calcium channel blockers and stimulants on morphine withdrawal in vitro. Eur. J. Pharmacol. **152:** 175–178, 1988.

BARRIOS, M., AND BAEYENS, J. M.: Differential effects of L-type calcium channel blockers and stimulants on naloxone-precipitated withdrawal in mice acutely dependent on morphine. Psychopharmacology **104:** 397–403, 1991.

BELLUZZI, J. D., GRANT, N., GARSKY, V., SARANTAKIS, D., WISE, C. D., AND STEIN, L.: Analgesia induced in vivo by central administration of enkephalin in the rat. Nature **260:** 625–626, 1976.

BENOLIEL, J. J., MAUBORGNE, A., BOURGOIN, S., LEGRAND, J. C., HAMON, M., AND CESSELIN, F.: Opioid control of the in vitro release of cholesystokinin-like material from the rat substantia nigra. J. Neurochem. **58:** 916–922, 1992.

BERGSTROM, L., AND TERENIUS, L.: Enkephalin levels decrease in rat striatum during morphine abstinence. Eur. J. Pharmacol. **60:** 349–352, 1979.

BHARGAVA, H. N.: Inhibition of naloxone-induced withdrawal in morphine dependent mice by l-trans-Δ 9-tetrahydrocannabinol. Eur. J. Pharmacol. **36:** 259–262, 1976a.

BHARGAVA, H. N.: Effects of some cannabinoids on naloxone-precipitated abstinence in morphine-dependent mice. Psychopharmacology **49:** 267–270, 1976b.

BHARGAVA, H. N.: Opioid-like action of methionine-enkephalin in inhibiting morphine abstinence syndrome. Eur. J. Pharmacol. **41:** 81–84, 1977a.

BHARGAVA, H. N.: Rapid induction and quantification of morphine dependence in the rat by pellet implantation. Psychopharmacology **52:** 55–62, 1977b.

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BHARGAVA, H. N.: The effects of naltrexone on the development of physical dependence on morphine. Eur. J. Pharmacol. **50:** 193–202, 1978a.

BHARGAVA, H. N.: New in vivo evidence for narcotic agonistic property of leucine-enkephalin. J. Pharm. Sci. **67:** 136–137, 1978b.

BHARGAVA, H. N.: Time course of the effects of naturally occuring cannabinoids on morphine abstinence syndrome. Pharmacol. Biochem. Behav. **8:** 7–11, 1978c.

BHARGAVA, H. N.: The effects of divalent ions on morphine analgesia and abstinence syndrome in morphine tolerant and dependent mice. Psychopharmacology **57:** 223–225, 1978d.

BHARGAVA, H. N.: Comparative effects of synthetic enkephalinamides and morphine on abstinence responses in morphine-dependents mice. Pharmacol. Biochem. Behav. **12:** 645–649, 1980a.

BHARGAVA, H. N.: The effects of thyrotropin releasing hormone on the central nervous system responses to chronic morphine administration. Psychopharmacology **68:** 185–189, 1980b.

BHARGAVA, H. N.: Cyclo (leucyl-glycine) inhibits the development of morphine-induced analgesic tolerance and dopamine receptor supersensitivity in rats. Life Sci. **27:** 117–123, 1980c.

BHARGAVA, H. N.: Inability of cyclo (leucyl-glycine) to facilitate the development of tolerance to and physical dependence on morphine in the rat. Life Sci. **27:** 1075–1081, 1980d.

BHARGAVA, H. N.: The effects of melanotropin release inhibiting factor and cyclo (Leu-Gly) on the tolerance to morphine-induced antinociception in the rat: a dose response study. Br. J. Pharmacol. **20:** 385–390, 1981a.

BHARGAVA, H. N.: The effect of peptides on tolerance to the cataleptic and hypothermic effects of morphine in the rat. Neuropharmacology **20:** 385–390, 1981b.

BHARGAVA, H. N.: Inhibition of tolerance to the pharmacological effects of human β-endorphin in the rat by prolyl-leucyl-glycinamide and cyclo (leucylglycine). J. Pharmacol. Exp. Ther. **218:** 404–408, 1981c.

BHARGAVA, H. N.: Enhanced response to apomorphine in rats treated with multiple injections of human β-endorphin and its blockade by Pro-Leu-Gly-NH_2 and cyclo (Leu-Gly). Life Sci. **29:** 1945–1949, 1981d.

BHARGAVA, H. N.: Dissociation of tolerance to the analgesic and hypothermic effects of morphine by using thyrotrophin releasing hormone. Life Sci. **29:** 1015–1020, 1981e.

BHARGAVA, H. N.: Inhibition of abstinence syndrome in opioid dependent mice by cyclo (His-Pro). Life Sci. **28:** 1261–1267, 1981f.

BHARGAVA, H. N.: Hypothalamic peptide hormone, prolyl-leucyl-glycinamide and analog inhibit tolerance to locomotor depressant but not to the locomotor stimulant action of morphine in the mouse. Neuropharmacology **21:** 227–233, 1982a.

BHARGAVA, H. N.: Effect of peptides on the development of tolerance to buprenorphine, a mixed opioid agonist-antagonist analgesic. Eur. J. Pharmacol. **79:** 117–123, 1982b.

BHARGAVA, H. N.: Binding of [^{3}H]spiroperidol to striatal membranes of rats treated chronically with morphine. Influence of Pro-Leu-Gly-NH_2 and cyclo (Leu-Gly). Neuropharmacology **22:** 1357–1361, 1983a.

BHARGAVA, H. N.: The effect of melanotropin release inhibiting factor, its metabolites and analogs on [^{3}H] apomorphine binding sites. Gen. Pharmacol. **14:** 609–614, 1983b.

BHARGAVA, H. N.: Peptides as drugs in the treatment of opioid addiction. *In* Opioid Peptides: Molecular Pharmacology Biosynthesis and Analysis, edited by R. S. Rapaka and R. L. Hawks, pp. 337–365, National Institute on Drug Abuse Research Monograph 70, Department of Health and Human Services publication no. (ADM) 86, Superintendent of Documents, U.S. Government Printing Office, Washington, DC, 1986a.

BHARGAVA, H. N.: The role of metabolism in the action of prolyl-leucyl-glycinamide on the development of tolerance to the analgesic effect of morphine. Neuropharmacology **25:** 737–741, 1986b.

BHARGAVA, H. N.: Intragastric administration of cyclo (Leu-Gly) inhibits the development of tolerance to the analgesic effect of morphine in the rat. Life Sci. **43:** 187–192, 1988.

BHARGAVA, H. N.: Opioid peptides, receptors and immune function. *In* Drugs of Abuse, Chemistry, Pharmacology, Immunology and AIDS, edited by P. T. K. Pham and K. C. Rice, pp. 220–233, National Institute on Drug Abuse Research Monograph 96, Department of Health and Human Services publication no. (ADM) 86, Superintendent of Documents, U.S. Government Printing Office, Washington, DC, 1990.

BHARGAVA, H. N.: Multiple opioid receptors of brain and spinal cord in opioid addiction. Gen. Pharmacol. **22:** 767–772, 1991a.

BHARGAVA, H. N.: Opioid systems and the immune function. *In* Stress and Immunity, edited by N. P. Plotnikoff, A. Murgo, R. E. Faith, and J. Wybran, pp. 329–342, CRC Press Inc., Boca Raton, FL, 1991b.

BHARGAVA, H. N.: Non-competitive antagonism of NMDA receptor inhibits tolerance to U-50,488H, a κ-opioid receptor agonist in the rat. Gen. Pharmacol, in press, 1994a.

BHARGAVA, H. N.: Nitric oxide synthase inhibition blocks tolerance to the analgesic action of κ-opiate receptor agonist in the rat. Pharmacology **48:** 234–241, 1994b.

BHARGAVA, H. N., AFIFI, A. H., AND WAY, E. L.: Effect of chemical sympathectomy on morphine antinociception and tolerance in the rat. Biochem. Pharmacol. **22:** 2769–2772, 1973.

BHARGAVA, H. N., AND DAS, S.: Evidence for opiate action at the brain receptors for thyrotropin releasing hormone. Brain Res. **368:** 262–267, 1986.

BHARGAVA, H. N., DAS, S., BANSINATH, M, AND PRASAD, R.: The binding of ^{3}H-(3-MeHis^2)thyrotropin releasing hormone to brain and pituitary membranes of morphine tolerant-dependent and abstinent rats. Pharmacol. Biochem. Behav. **34:** 7–12, 1989a.

BHARGAVA, H. N., DAS, S., AND GULATI, A.: Stereoselectivity of kappa opiate receptor ligands in inhibiting the binding of ^{3}H-(3-MeHis^2) thyrotropin releasing hormone to brain membranes. J. Pharm. Pharmacol. **40:** 70–72, 1988.

BHARGAVA, H. N., AND GULATI, A.: Down-regulation of brain and spinal cord μ-opioid in morphine tolerant-dependent rats. Eur. J. Pharmacol. **190:** 305–311, 1990a.

BHARGAVA, H. N., AND GULATI, A.: Modification of brain and spinal cord dopamine D_1 receptors labeled with ^{3}H-SCH 23390 following morphine withdrawal from tolerant and physically dependent rats. J. Pharmacol. Exp. Ther. **252:** 901–907, 1990b.

BHARGAVA, H. N., GULATI, A., AND RAHMANI, N. H.: Differences in the binding of [^{3}H] [D-Ser^2, Thr^6] leucine enkephalin and [^{3}H] [D-Pen^2, D-Pen^5] enkephalin to brain membranes of morphine tolerant-dependent rats. Eur. J. Pharmacol. **202:** 403–406, 1991a.

BHARGAVA, H. N., GULATI, A., AND RAHMANI, N. H.: Effect of morphine tolerance-dependence and abstinent on κ-opioid receptors of rat brain and spinal cord. Biochem. Pharmacol. **42:** 1302–1306, 1991b.

BHARGAVA, H. N., GULATI, A., AND RAMARAO, P.: Effect of chronic administration of U-50–488H on tolerance to its pharmacological actions and on multiple opioid receptors in rat brain regions and spinal cord. J. Pharmacol. Exp. Ther. **251:** 21–26, 1989b.

BHARGAVA, H. N., GULATI, A., AND RAMARAO, P.: Binding characteristics of [^{3}H] SCH 23390 in spinal cord and discrete brain regions of kappa-opiate tolerant-dependent and abstinent rats. Pharmacology **42:** 121–127, 1991c.

BHARGAVA, H. N., AND KIM, H. S.: Structure-activity relationship studies with hypothalamic peptide hormones. I. Effect of melanotropin release inhibiting factor and analogs on tolerance to morphine in the rat. J. Pharmacol. Exp. Ther. **220:** 394–398, 1982.

BHARGAVA, H. N., AND MATWSYHYN, G. A.: Brain serotonin turnover and morphine tolerance-dependence induced by multiple injections in the rat. Eur. J. Pharmacol. **44:** 25–33, 1977.

BHARGAVA, H. N., AND MATWSYHYN, G. A.: Comparative effects of thyrotropin releasing hormone, MK-771 and DN-1417 on morphine abstinence syndrome. Psychopharmacology **87:** 141–146, 1985.

BHARGAVA, H. N., AND MATWSYHYN, G. A.: Dizocilpine (MK-801) blocks the tolerance to the analgesic but not to the hyperthermic effect of morphine in the rat. Pharmacology **47:** 344–350, 1993.

BHARGAVA, H. N., MATWYSHYN, G. A., GERK, P. M., BOZEK, P. S., BAILEY, M. D., KO, K. H., SIMKO, R. J., AND THORAT, S. N.: Effect of naltrexone pellet implantation on morphine tolerance and physical dependence in the rat. Gen. Pharmacol. **25:** 149–155, 1994a.

BHARGAVA, H. N., MATWYSHYN, G. A., AND RAMARAO, P.: The effect of U-50,488H, a κ-opioid receptor agonist on tolerance to the analgesic and hyperthermic effects of morphine in the rat. Gen. Pharmacol. **22:** 429–434, 1991d.

BHARGAVA, H. N., MATWYSHYN, G. A., RATTAN, A. K., KOO, K. L., AND TEJWANI, G. A.: The effect of U-50,488H tolerance-dependence and abstinence on the levels of dynorphin$_{1-13}$ in discrete brain regions, spinal cord, pituitary gland and peripheral tissues of the rat. Brain Res. **600:** 151–155, 1993.

BHARGAVA, H. N., MATWYSHYN, G. A., RATTAN, A. K., KOO, K. L. AND TEJWANI, G. A.: β-endorphin-like immunoreactivity in discrete brain regions, spinal cord and peripheral tissues of U-50,488H tolerant and abstinent rats. J. Pharmacol. Exp. Ther. **268:** 856–861, 1994b.

BHARGAVA, H. N., PANDEY, R. N., AND MATWYSHYN, G. A.: Effects of prolyl-leucyl-glycinamide and cyclo (Leu-Gly) on morphine induced antinociception and brain μ, δ and κopioid receptors. Life Sci. **32:** 2095–2101, 1983.

BHARGAVA, H. N., AND RAMARAO, P.: Comparative effects of Pro-Leu-Gly-NH_2 and cyclo (Leu-Gly) administered orally on the development of tolerance to the analgesic effect of morphine in the rat. Peptides **10:** 767–771, 1989a.

BHARGAVA, H. N., AND RAMARAO, P.: Antagonism of kappa opioid mediated effects in the rat by cyclo (Leu-Gly). Life Sci. **45:** 2521–2528, 1989b.

BHARGAVA, H. N., AND RAMARAO, P.: The effect of Panax ginseng on the development of tolerance to the pharmacological actions of morphine in the rat. Gen. Pharmacol. **22:** 521–525, 1991.

BHARGAVA, H. N., RAMARAO, P. AND GULATI, A.: Effects of morphine in rats treated chronically with U-50,488H, a kappa opioid receptor agonist. Eur. J. Pharmacol. **162:** 257–264, 1989a.

BHARGAVA, H. N., RAMARAO, P., GULATI, A., GUDEHITHLU, K. P., AND TEJWANI, G. A.: Methionine-enkephalin and β-endorphin levels in spleen and thymus gland of morphine tolerant-dependent and abstinent rats. Life Sci. **45:** 2529–2537, 1989b.

BHARGAVA, H. N., REDDY, P. L., AND GUDEHITHLU, K. P.: Down-regulation of N-methyl-D-aspartate (NMDA) receptors of brain regions and spinal cord of rats treated chronically with morphine. Gen. Pharmacol, in press, 1994c.

BHARGAVA, H. N., THOMAS, P. T., THORAT, S. N., AND HOUSE, R. V.: Effect of morphine tolerance and abstinence on the cellular immune function. Brain Res., **642:** 1–10, 1994d.

BHARGAVA H. N., AND THORAT, S. N.: Effect of dizocilpine (MK-801) on analgesia and tolerance induced by U-50,488H, a κ-opioid receptor agonist, in the mouse. Brain Res., **649:** 111–116, 1994.

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BHARGAVA, H. N., WALTER, R., AND RITZMANN, R. F.: Development of narcotic tolerance and physical dependence effects of Pro-Leu-Gly-NH_2 and cyclo (Leu-Gly). Pharmacol. Biochem. Behav. **12:** 73–77, 1980.

BHARGAVA, H. N., AND WAY, E. L.: Acetylcholinesterase inhibition and morphine effects in morphine tolerance and dependent mice. J. Pharmacol. Exp. Ther. **183:** 31–40, 1972.

BHARGAVA, H. N., AND WAY, E. L.: Effect of 1-phenyl-3-(2-thiazolyl)-2-thiourea (PTT), a dopamine β-hydroxylase (DβH) inhibitor on morphine analgesia, tolerance and physical dependence. J. Pharmacol. Exp. Ther. **190:** 165–175, 1974.

BHARGAVA, H. N., AND WAY, E. L.: Brain acetylcholine and choline changes following acute and chronic morphinization and during withdrawal. J. Pharmacol. Exp. Ther. **194:** 65–73, 1975.

BICKEL, W. K., STITZER, M. L., BIGELOW, G. E., LIEBSON, I. A., JASINSKI, D. R., AND JOHNSON, R. E.: A clinical trial of buprenorphine: comparison with methadone in the detoxification of heroin addicts. Clin. Pharmacol. Ther. **43:** 72–78, 1988a.

BICKEL, W. K., STITZER, M. L., BIGELOW, G. E., LIEBSON, I. A., JASINSKI, D. R., AND JOHNSON, R. E.: Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. J. Pharmacol. Exp. Ther. **247:** 47–53, 1988b.

BLALOCK, J. E., AND SMITH, E. M.: Human leukocytic interferon: structural and biological relatedness to adrenocorticotropic hormone and endorphins. Proc. Natl. Acad. Sci. USA **77:** 5972–5974, 1980.

BLALOCK, J. E., AND SMITH, E. M.: Human leukocytic interferon (HuIFN-α): potent endorphin like opioid activity. Biochem. Biophys. Res. Commun. **101:** 472–478, 1981.

BLASIG, J., HERZ, A., REINOLD, K., AND ZIEGELGANSBERGER, S.: Development of physical dependence on morphine in respect to time and dosage and quantification of the precipitated withdrawal syndrome in rats. Psychopharmacologia **33:** 19–38, 1973.

BONGIANNI, F., CARLA, V., MORONI, F., PELLEGRINI, AND GIAMPIETRO, D. E.: Calcium channel inhibitors suppress the morphine withdrawal syndrome in rats. Br. J. Pharmacol. **88:** 561–567, 1986.

BOWERS, C. Y., FRIESEN, H. G., WANG, P., GUYDA, H. J., AND FOLKERS, K.: Prolactin and thyrotrophin release in man by synthetic pyroglutamyl histidyl-prolinamide. Biochem. Biophys. Res. Commun. **45:** 1033–1041, 1971.

BRAESTRUP, C., AND SQUIRES, R. F.: Specific benzodiazepine receptors in the rat brain characterised by high affinity ^{3}H-diazepam binding. Proc. Natl. Acad. Sci. USA **74:** 3805–3809, 1977.

BRASE, D. A., TSENG, L. E., LOH, H. H., AND WAY, E. L.: Cholinergic modification of naloxone-jumping in morphine dependent mice. Eur. J. Pharmacol. **26:** 1–8, 1974.

BREDT, D. S., AND SNYDER, S. H.: Nitric oxide, a novel neuronal messenger. Neuron **8:** 3–11, 1992.

BROMAGE, P. R., CAMPORESI, E., AND CHESTNUT, D.: Epidural narcotics for post-operative analgesia. Anesth. Analg. **59:** 473–480, 1980.

BROWN, G. R.: Stadol dependence: another case. J. Am. Med. Assoc. **254:** 910, 1985.

BROWN, S. M., STIMMEL, B., TAUB, R. N., KOCHWA, S., AND ROSENFIELD, R. E.: Immunologic dysfunction in heroin addicts. Arch. Intern. Med. **134:** 1001–1006, 1974.

BRYANT, H. U., BERNTON, E. W., AND HOLADAY, J. W.: Morphine pellet-induced immunomodulation in mice: temporal relationships. J. Pharmacol. Exp. Ther. **245:** 913–114, 1988.

BRYANT, H. U., AND ROUDEBUSH, R. E.: Suppressive effects of morphine pellet implants on in vivo parameters of immune function. J. Pharmacol. Exp. Ther. **255:** 410–414, 1990.

BUCCAFUSCO, J. J., MARSHALL, D. C., AND TARNER, R. M.: A comparison of the inhibitory effects of clonidine and guanfacine on the behavioral and autonomic components of morphine withdrawal in rats. Life Sci. **35:** 1401–1408, 1984.

BURTON, C. K., HO, I. K., AND HOSKINS, B.: Effect of cyclo (Leu-Gly) on cyclic GMP-phosphodiesterase activity changes associated with development of tolerance to morphine induced antinociception, catalepsy, respiratory depression and mydriasis. J. Pharmacol. Exp. Ther. **258:** 871–876, 1991.

BUSCHER, H. H., HILL, R. C., ROMER, D., CARDINAUX, F., CLOSSE, A., HAUSER, D., AND PLESS, J.: Evidence for analgesic activity of enkephalin in the rat. Nature **261:** 423–425, 1976.

CAPPENDIJK, S. L. T., DEVRIES, R., AND DZOLJIC, M. R.: Inhibitory effect of nitric oxide (NO) synthase inhibitors on nalxone-precipitated withdrawal syndrome in morphine-dependent mice. Neurosci. Lett. **162:** 97–100, 1993.

CARDENAS, H. L., AND ROSS, D. H.: Morphine induced calcium depletion in discrete regions of rat brain. J. Neurochem. **24:** 487–493, 1975.

CARDENAS, H. L., AND ROSS, D. H.: Calcium depletion of synaptosomes after morphine treatment. Br. J. Pharmacol. **57:** 521–526, 1976.

CARO, G., BARRIOS, M., AND BAEYENS, J. M.: Dose-dependent and stereoselective antagonism by diltiazem of naloxone-precipitated morphine abstinence after acute morphine-dependence in vivo and in vitro. Life Sci. **43:** 1523–1527, 1988.

CERVO, L., ROCHAT, C., ROMANDINI, S. AND SAMANIN, R.: Evidence of a preferential role of brain serotonin in the mechanisms leading to naloxone precipitated compulsive jumping in morphine-dependent rats. Psychopharmacology **74:** 271–274, 1981.

CHAPMAN, D. B., HU, J., AND WAY, E. L.: Methionine-enkephalin antagonism and endorphin potentiation of narcotic induced analgesia. Eur. J. Pharmacol. **65:** 369–371, 1980.

CHARNEY, D. S., REDMOND, D. E., GALLOWAY, M. P., KLEBER, H. D., HENINGER, G. R., MURBERG, M., AND ROTH, R. H.: Naltrexone precipitated opioid withdrawal in methadone addicted human subjects: evidence for adrenergic hyperactivity. Life Sci. **35:** 1263–1272, 1984.

CHAVKIN, C., AND GOLDSTEIN, A.: Specific receptor for the opioid peptide dynorphin: structure-activity relationships. Proc. Natl. Acad. Sci. USA **78:** 6543–6547, 1981.

CHENEY, D. L., AND GOLDSTEIN, A.: The effect of p-chloro-phenylalanine on opiate-induced running, analgesia, tolerance and physical dependence in mice. J. Pharmacol. Exp. Ther. **177:** 309–315, 1971.

CHIPKIN, R. E., BERGER, J. G., BILLARD, W., IORIO, L. C., CHAPMAN, R., AND BARNETT, A.: Pharmacology of SCH 34826, an orally active enkephalinase inhibitor analgesic. J. Pharmacol. Exp. Ther. **245:** 829–838, 1988.

CLEMENTI, G., VALERIO, C., PRATO, A., CARUSO, A., PATTI, F., PATANE, AND DRAGO, F.: Effects of calcitonin on morphine tolerance and withdrawal syndrome in morphine physically dependent rats. Eur. J. Pharmacol. **163:** 175–179, 1989.

CLEMENT-JONES, V., MCLOUGHLIN, L., LOWRY, P. J., BESSER, G. M., REES, L. H., AND WEN, H. L.: Acupuncture in heroin addicts: changes in met-enkephalin and β-endorphin in blood and cerebrospinal fluid. Lancet **2:** 380–382, 1979.

COCHIN, J., AND KORNETSKY, C.: Development and loss of tolerance to morphine in the rat after single and multiple injections. J. Pharmacol. Exp. Ther. **145:** 1–10, 1964.

CORBETT, A. D., PATERSON, S. J. MCKNIGHT, A. T., MAGNAN, J., AND KOSTERLITZ, H. W.: Dynorphin$_{1-8}$ and dynorphin$_{1-9}$ are ligands for the κ-subtype of opiate receptor. Nature **299:** 79–81, 1982.

COSTA, T., AKORIES, K., SCHULZ, G., AND WUSTER, M.: Pertussis toxin decreases opioid receptor binding and adenylate cyclase inhibition in a neuroblastoma × glioma hybrid cell lines. Life Sci. **33:** 219–222, 1983.

DAFNY, N.: Modification of morphine withdrawal by interferon. Life Sci. **32:** 303–305, 1983.

DAFNY, N., WAGLE, V. G., AND DRATH, D. B.: Cyclosporine alters opioid withdrawal in rodents. Life Sci. **36:** 1721–1726, 1985.

DAS, S., AND BHARGAVA, H. N.: The effect of chronic morphine treatment on striatal ^{3}H-N-propylnorapomorphine binding in the rat: influence of prolyl-leucyl-glycinamide. Pharmacology **31:** 241–247, 1985.

DAS, S., AND BHARGAVA, H. N.: Effects of Pro-Leu-Gly-NH_2 and cyclo (Leu-Gly) on the binding of ^{3}H-quinuclidinyl benzilate to the striatal cholinergic muscarinic receptors. Peptides **7:** 21–25, 1986.

DAS, S., AND BHARGAVA, H. N.: Unidirectional interaction between thyrotropin releasing hormone and opiates at the level of their brain receptors. Gen. Pharmacol. **18:** 99–102, 1987a.

DAS, S., AND BHARGAVA, H. N.: Inhibition of ^{3}H-(3-MeHis^2) thyrotropin releasing hormone recognition sites in the brain by tifluadom, a kappa opiate agonist. Neuropharmacology **26:** 1141–1146, 1987b.

DAS, S., MATWYSHYN, G. A., AND BHARGAVA, H. N.: The binding of ^{3}H-quinuclidinyl benzilate to cholinergic muscarinic receptors in rat brain regions following chronic treatment with morphine and during abstinence. Neuropeptides **5:** 45–48, 1984.

DEECHER, D. C., TEITLER, M., SODERLUND, D. M., BORNMANN, W. G., KUEHNE, M. E., AND GLICK, S. D.: Mechanisms of action of ibogaine and harmaline congeners based on radiological binding studies. Brain Res. **571:** 242–247, 1992.

DEL POZO, E., CARO, G., AND BAEYENS, J. M.: Analgesic effect of calcium blockers in mice. Eur. J. Pharmacol. **137:** 155–160, 1987.

DENEAU, G., YANAGITA, T., AND SEEVERS, M. H.: Self-administration of psychoactive substances by the monkey. A measure of psychological dependence. Psychopharmacologia **16:** 30–48, 1969.

DHAHIR, H. I.: A Comparative Study of the Toxicity of Ibogaine and Serotonin. Doctoral thesis, Ann Arbor, MI, University Microfilm Intern. **71:** 25–341, 1971.

DIB, B., AND DUCLAUX, R.: Intracerebroventricular self-injection of morphine in response to pain in the rat. Pain **13:** 395–406, 1982.

DI CHIARA, G., AND IMPERATO, A.: Drugs abused by humans preferentially increase synaptic dopamine concentration in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. USA **85:** 5274–5277, 1988.

DICKENSON, A. H., AND KNOX, R. J.: Antagonism of μ-opioid receptor mediated inhibitions of nociceptive neurons by U-50,488H and dynorphin (1–13) in the rat dorsal horn. Neurosci. Lett. **75:** 229–234, 1987.

DIONYSSOPOULOS, T., HOPE, W., AND COUPAR, I. M.: Effect of adenosine analogues on the expression of opioid withdrawal in rats. Pharmacol. Biochem. Behav. **42:** 201–206, 1992.

DOCKRAY, G. J., AND WILLIAMS, R. G.: FMRF-amide like immunoreactivity in rat brain: development of radioimmunoassay and its application in studies of distribution and chromatographic properties. Brain Res. **266:** 295–303, 1983.

DOLE, V. P., NYSWANDER, M. E., AND KREEK, M. J.: Narcotic blockade. Arch. Intern. Med. **118:** 304–309, 1966.

DOLPHIN, A. C.: Nucleotide binding protein in signal transduction and disease. Trends Neurosci. **10:** 53–57, 1987.

DOMINO, E. F., AND WILSON, A. E.: Enhanced brain acetylcholine utilization during morphine withdrawal in the rat. Nature **243:** 285–286, 1973.

DOMINO, E. F., AND WILSON, A. E.: Brain acetycholine in morphine pellet implanted rats given naloxone. Psychopharmacology **41:** 19–22, 1975.

DOURISH, C. T., HAWLEY, D., AND IVERSEN, S. D.: Enhancement of morphine

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analgesia and prevention of morphine tolerance in the rat by the cholecystokinin antagonist, L-364,718. Eur. J. Pharmacol. **147:** 469–472, 1988.

DOURISH, C. T., O'NEILL, M. F., COUGHLAN, J., KITCHENER, S. J., HAWLEY, D., AND IVERSEN, S. D.: The selective CCK-B receptor antagonist L-365,260 enhances morphine analgesia and prevents morphine tolerance in the rat. Eur. J. Pharmacol. **176:** 35–44, 1990.

DRUMMOND, D. C., TAYLOR, J. A., AND MULLIN, P. I.: Replacement of a prescribing service by an opioid-free day programme in a Glasgow drug clinic. Br. J. Addict. **81:** 559–565, 1986.

DRUMMOND, D. C., TURKINGTON, D., RAHMAN, M. Z., MULLIN, J., AND JACKSON, P.: Chlordiazepoxide vs. methadone in opioid withdrawal: a preliminary double-blind trial. Drug Alcohol Depend. **23:** 63–72, 1989.

DZOLJIC, M. R., BOKSANSKA, A., KORENHOF, A. M., KAPLAN, C. D., DZOLJIC M., RUPRESHT, J., ZIJLSTRA, F. N., BRINKMAN, E. C. A., AND CAPPENDIJK, S. L. T.: The effects of orally active enkephalinase inhibitors on morphine withdrawal syndrome. Neuroreport **3:** 637–640, 1992.

DZOLJIC, E. D., KAPLAN, C. D., AND DZOLJIC, M. R.: Effect of ibogaine on naloxone-precipitated withdrawal syndrome in chronic morphine-dependent rats. Arch. Int. Pharmacodyn. Ther. **294:** 64–70, 1988.

DZOLJIC, M. R., RADEMAKER, B., POEL-HEISTERKAMP, A. L., UKPONMWAN, O. E., AND HAFFMANS, J.: Enkephalinase inhibition suppresses naloxone-induced jumping in morphine-dependent mice. Arch. Int. Pharmacodyn. Ther. **283:** 222–228, 1986.

EDDY, N. B., PILLER, M., PIRK, L. A., SHRAPPE, O., AND WENDER, S.: The effect of the addition of a narcotic antagonist on the rate of development of tolerance. Bull. Narc. **12:** 1–16, 1960.

ELSWORTH, J. D., REDMOND, D. E., JR., AND ROTH, R. H.: Effect of morphine treatment and withdrawal on endogenous methionine- and leucine-enkephalin levels in primate brain. Biochem. Pharmacol. **35:** 3415–3417, 1986.

FARIS, P. L., KAMISARUK, B. R., WATKINS, L. R., AND MAYER, D. J.: Evidence for the neuropeptide cholecystokinin as an antagonist of opioid analgesia. Science **219:** 310–312, 1983.

FOLKESSON, R., MONSTEIN, H-J., GELJER, T., AND TERENIUS, L.: Modulation of proenkephalin A gene expression by cyclic AMP. Mol. Brain Res. **5:** 211–217, 1989.

FRIEDLER, G., BHARGAVA, H. N., QUOCK, R., AND WAY, E. L.: The effect of 6-hydroxy-dopamine on morphine tolerance and physical dependence. J. Pharmacol. Exp. Ther. **183:** 49–55, 1972.

FRIEDMAN, H. J., JEN, M. F., CHANG, J. K., LEE, N. M., AND LOH, H. H.: Dynorphin: a possible modulatory peptide on morphine or β-endorphin analgesia in mouse. Eur. J. Pharmacol. **69:** 357–360, 1981.

FUDALA, P. J., JAFFE, J. H., DARX, E. M., AND JHONSON, R. E.: Use of buprenorphine in the treatment of opioid addiction. II. Physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. Clin. Pharmacol. Ther. **47:** 525–534, 1990.

FUKAGAWA, Y., KATZ, J. L., AND SUZUKI, T.: Effects of a selective k-opioid agonist, U-50,488H on morphine dependence in rats. Eur. J. Pharmacol. **170:** 47–51, 1989.

GIBERT-RAHOLA, J., MALDONADO, R., MICO, J. A., LEONSEQUI, I., AND SAAVEDRA, M. C.: Comparative studies in mice of flunitrazepam vs. diazepam on morphine withdrawal syndrome. Prog. Neuropsychopharmacol. Biol. Psychiatry **12:** 927–933, 1988.

GLICK, S. D., COX, R. S., AND CRANE, A. M.: Changes in morphine self-administration and morphine dependence after lesions of the caudate nucleus in rats. Psychopharmacologia **41:** 219–224, 1975.

GLICK, S. D., ROSSMAN, K., RAO, N. C., MAISONNEUVE, I. M., AND CARLSON, J. N.: Effects of ibogaine on acute signs of morphine withdrawal in rats: independence from tremor. Neuropharmacology **31:** 497–500, 1992.

GLICK, S. D., ROSSMAN, K., STEINDORF, S., MAISONNEUVE, I. M., AND CARLSON, J. N.: Effects and aftereffects of ibogaine on morphine self-administration. Eur. J. Pharmacol. **195:** 341–345, 1991.

GMEREK, D. E., KATZ, J. L., FRANCE, C. P., AND WOODS, J. H.: Systemic and intracerebroventricular effects of opioid peptides in withdrawn morphine-dependent rhesus monkeys. Life Sci. **33:** 361–364, 1983.

GOLD, M. S., REDMOND, D. E., JR., AND KLEBER, H. D.: Clonidine blocks acute opiate-withdrawal symptoms. Lancet **2:** 599–601, 1978.

GOLD, M. S., REDMOND, D. E., JR., AND KLEBER, H. D.: Noradrenergic hyperactivity in opioid withdrawal. Am. J. Psychiatry **136:** 100–102, 1979.

GOLDSTEIN, A., FISCHLI, W., LOWNEY, L. I., HUNKAPILLER, M., AND HOOD, L.: Porcine pituitary dynorphin: complete amino acid sequences of the biologically active heptadecapeptide. Proc. Natl. Acad. Sci. USA **78:** 7219–7223, 1981.

GOLDSTEIN, A., TACHIBANA, S., LOWNEY, L. I., HUNKAPILLER, M., AND HOOD, L.: Dynorphin (1–13), an extraordinary potent opioid peptide. Proc. Natl. Acad. Sci. USA **76:** 6666–6670, 1979.

GOMAA, A. A., MOHAMED, L. H., AND AHMED, H. N.: Modification of morphine-induced analgesia, tolerance and dependence by bromocryptine. Eur. J. Pharmacol. **170:** 129–135, 1989.

GREEN, P. G., AND LEE, N. M.: Dynorphin A-(1–13) attenuates withdrawal in morphine-dependent rats: effect of route of administration. Eur. J. Pharmacol. **145:** 267–272, 1988.

GUDEHITHLU, K. P., AND BHARGAVA, H. N.: Differential changes in preproenkephalin in brain regions and spinal cord of morphine-tolerant and abstinent rats. FASEB J. **8:** A379, 1994.

GUDEHITHLU, K. P., REDDY, P. L., AND BHARGAVA, H. N.: Effect of chronic morphine treatment on the binding of ^{3}H-MK-801 to rat brain and spinal cord membranes. Pharmacologist **35:** A190, 1993.

GUDEHITHLU, K. P., REDDY, P. L., AND BHARGAVA, H. N.: Effect of morphine tolerance and abstinence on the binding of ^{3}H-MK-801 to rat brain regions and spinal cord of the rat. Brain Res. **639:** 269–274, 1994.

GUDEHITHLU, K. P., TEJWANI, G. A., AND BHARGAVA, H. N.: β-Endorphin and methionine-enkephalin levels in discrete brain regions, spinal cord, pituitary gland and serum of morphine tolerant-dependent and abstinent rats. Brain Res. **553:** 284–290, 1991.

GULATI, A., AND BHARGAVA, H. N.: Cerebral cortical 5-HT$_1$ and 5-HT$_2$ receptors of morphine tolerant-dependent rats. Neuropharmacology **27:** 1231–1237, 1988.

GULATI, A., AND BHARGAVA, H. N.: Brain and spinal cord 5-HT$_2$ receptors of morphine tolerant-dependent and abstinent rats. Eur. J. Pharmacol. **167:** 185–192, 1989.

GULATI, A., AND BHARGAVA, H. N.: Down-regulation of hypothalamic 5-HT$_{1A}$ receptors in morphine-abstinent rats. Eur. J. Pharmacol. **182:** 253–259, 1990.

GULATI, A., RAMARAO, P., AND BHARGAVA, H. N.: Effect of repeated administration of U-50,488H, a kappa opioid receptor agonist, on central 5-HT$_1$ and 5-HT$_2$ receptors in the rat. Pharmacology **39:** 145–153, 1989.

HAFFMANS, J., AND DZOLJIC, M. R.: Inhibition of enkephalinase activity attenuates naloxone-precipitated withdrawal symptoms. Gen. Pharmacol. **18:** 103–105, 1987.

HAMBURG, M., AND TALLMAN, J. F.: Chronic morphine administration increases the apparent number of α_2-adrenergic receptors in rat brain. Nature **291:** 493–495, 1981.

HARRIS, R. A., LOH, H. H., AND WAY, E. L.: Effects of divalent ions, cation chelators and an ionophore on morphine analgesia and tolerance. J. Pharmacol. Exp. Ther. **195:** 488–498, 1975.

HARRIS, R. A., YAMAMOTO, H., LOH, H. H., AND WAY, E. L.: Discrete changes in brain calcium with morphine analgesia, tolerance-dependence and abstinence. Life Sci. **20:** 501–506, 1977.

HEBERMAN, R. B., ORTALDO, J. R., AND BONNARD, G. D.: Augmentation by interferon of human natural and antibody-dependent cell mediated cytotoxicity. Nature **277:** 221–223, 1979.

HERMAN, B. H., AND GOLDSTEIN, A.: Antinociception and paralysis induced by intrathecal dynorphin A. J. Pharmacol. Exp. Ther. **232:** 27–32, 1985.

HESCHELER, J., ROSENTHAL, W., TRAUTEIN, W., AND SCHULZ, G.: GTP-binding protein-G$_o$ regulates neuronal calcium channels. Nature **325:** 445–447, 1987.

HINE, B., TORRELIO, M., AND GERSHON, S.: Interactions between cannabidiol and Δ^9-THC during abstinence in morphine-dependent rats. Life Sci. **17:** 851–858, 1975.

HO, A. K. S., CHEN, R. C. A., AND KREEK, M. J.: Morphine withdrawal in the rat: assessment by quantitation of diarrhea and modification by ethanol. Pharmacology **18:** 9–17, 1979.

HO, I. K., BRASE, D. A., LOH, H. H., AND WAY, E. L.: Influence of l-tryptophan on morphine analgesia, tolerance and physical dependence. J. Pharmacol. Exp. Ther. **193:** 35–43, 1975.

HO, I. K., LOH, H. H., AND WAY, E. L.: Influence of 5, 6-dihydroxytryptamine on morphine tolerance and physical dependence. Eur. J. Pharmacol. **21:** 331–336, 1973a.

HO, I. K., LOH, H. H., AND WAY, E. L.: Effects of cyclic 3′, 5′-adenosine monophosphate on morphine tolerance and physical dependence. J. Pharmacol. Exp. Ther. **185:** 347–357, 1973b.

HO, I. K., LOH, H. H., AND WAY, E. L.: Pharmacological manipulation of gamma aminobutyric acid (GABA) in morphine analgesia, tolerance and physical dependence. Life Sci. **18:** 1111–1124, 1976.

HO, I. K., LU, S. E., STOLMAN, S., LOH, H. H. AND WAY, E. L.: Influence of *p*-chlorophenylalanine on morphine tolerance and physical dependence and regional brain serotonin turnover studies in morphine tolerant-dependent mice. J. Pharmacol. Exp. Ther. **182:** 155–165, 1972.

HO, W. K. K., WEN, H. L., AND LING, N.: β-Endorphin-like immunoreactivity in the plasma of heroin addicts and normal subjects. Neuropharmacology **19:** 117–120, 1980.

HOLADAY, J. W., TSENG, L. F., LOH, H. N., AND LI, C. H.: Thyrotrophin releasing hormone antagonizes beta-endorphin hypothermia and catalepsy. Life Sci. **22:** 1537–1544, 1978.

HOLLT, V., PRZEWLOCKI, R., AND HERZ, A.: Beta-endorphin like immunoreactivity in plasma, pituitaries and hypothalamus of rats following treatment with opioid. Life Sci. **23:** 1057–1066, 1978.

HOLZ, G. G., RANE, S. G., AND DUNLAP, K.: GTP-binding proteins mediate transmitter inhibition of voltage-dependent calcium channels. Nature **319:** 670–672, 1986.

HORITA, A., CARINO, M. A., AND CHESTNUT, R. M.: Influence of thyrotropin-releasing hormone on drug-induced narcosis and hypothermia in rabbits. Psychopharmacology **49:** 57–62, 1976.

HOYER, D., AND SCHOEFFTER, P.: 5-HT receptors: subtypes and second messengers. J. Recept. Res. **11:** 197–214, 1991.

HUDDLESTONE, J. R., MERIGAN, T. C., AND OLDSTONE, M. B.: Induction and kinetics of natural killer cells in humans following interferon therapy. Nature **282:** 417–419, 1979.

HUGHES, J., HUNTER, J. C., AND WOODRUFF, G. N.: Neurochemical actions of CCK underlying the therapeutic potential of CCK-B antagonists. Neuropeptides **19:** 85–89, 1991.

HUGHES, J., SMITH, T. W., KOSTERLITZ, H. W., FOTHERGILL, L. A., MORGAN,

PHARM REV
PHARMACOLOGICAL REVIEWS
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B. A., AND MORRIS, H. R.: Identification of two related pentapeptides from the brain with potent opioid agonist activity. Nature 258: 577–579, 1975.
HUNG, C. Y., LEFKOWITZ, S. S., AND GEBER, W. F.: Interferon inhibition by narcotic analgesic. Proc. Soc. Exp. Biol. Med. 142: 106–111, 1973.
HYNES, M. D., MCCARTEN, M. D., SHEARMAN, G., AND LAL, H.: Differential reduction of morphine withdrawal body shakes by butaclamol enantioners. Life Sci. 22: 133–136, 1978.
HYNES, M. D., GIANUTSOS, G., AND LAL, H.: Effects of cholinergic agonists and antagonists on morphine-withdrawal syndrome. Psychopharmacology 49: 191–195, 1976.
JACQUET, Y. F.: NMDA receptor: central role in pain inhibition in rat periaqueductal gray. Eur. J. Pharmacol. 154: 271–276, 1988.
JASINSKI, D. R., PEVNICK, J. S., AND GRIFFITH, J. D.: Human pharmacology and abuse potential of the analgesic buprenorphine. Arch. Gen. Psychiatry 35: 501–516, 1978.
JAW, S. P., HOSKINS, B., AND HO, I. K.: Involvement of δ-opioid receptors in physical dependence on butorphanol. Eur. J. Pharmacol. 240: 67–72, 1993a.
JAW, S. P., MAKIMURA, M., HOSKINS, B., AND HO, I. K.: Effects of norbinaltorphimine on butorphanol dependence. Eur. J. Pharmacol. 239: 133–140, 1993b.
JOHNSON, R. E., CONE, E. J., HENNINGFIELD, J. E., AND FUDALA, P. J.: Use of buprenorphine in the treatment of opiate addiction. I. Physiologic and behavioral effects during a rapid dose-reduction. Clin. Pharmacol. Ther. 46: 335–543, 1989.
JURNA, I., AND ZETLER, G.: Antinociceptive effects of centrally administered caerulein and cholecystokinin octapeptide (CCK-8). Eur. J. Pharmacol. 73: 323–331, 1981.
KAKUNAGA, T., KANETO, H., AND HANO, K.: Pharmacological studies on analgesia-VII. Significance of the calcium ion in morphine analgesia. J. Pharmacol. Exp. Ther. 153: 134–141, 1966.
KARKALAS, J., AND LAL, H.: A comparison of haloperidol with methadone in blocking heroin withdrawal symptoms. Int. J. Pharmacopsychiatry 8: 248–251, 1973.
KEBABIAN, J. W., AND CALNE, D. B.: Multiple receptors for dopamine. Nature 277: 93–96, 1979.
KELLSTEIN, D. E., AND MAYER, D. J.: Spinal co-administration of cholecystokinin antagonists with morphine prevents the development of opioid tolerance. Pain 47: 221–229, 1991.
KELLSTEIN, D. E., PRICE, D. D., AND MAYER, D. J.: Cholecystokinin and its antagonist lorglumide respectively attenuate and facilitate morphine induced inhibition of C-fiber evoked discharges of dorsal horn nociceptive neurons. Brain Res. 540: 302–306, 1991.
KESNER, R. P., AND PRIANO, D. J.: Disruptive effects of naloxone on development of morphine tolerance. Life Sci. 21: 509–512, 1977.
KEST, B., MAREK, P., AND LIEBESKIND, J. C.: The specific N-methy-D-aspartate (NMDA) receptor antagonist MK-801 blocks U-50,488H, but not morphine antinociception. Brain Res. 589: 139–142, 1992.
KHAVARI, K. A., AND RISNER, M. E.: Opioid dependence produced by ad libitum drinking of morphine in water, saline and sucrose vehicles. Psychopharmacologia 30: 291–302, 1973a.
KHAVARI, K. A., AND RISNER, M. E.: Concentration-ingestion relations of morphine-adulterated food and morphine solution. Psychopharmacologia 30: 45–60, 1973b.
KIM, H. S., OH, K. W., PARK, W. K., YAMANO, S., AND TOKI, S.: Effects of Panax ginseng on the development of morphine tolerance and dependence and on antagonism of morphine analgesia. Korean J. Ginseng Sci. 11: 182–190, 1987.
KIMES, A. S., VAUPEL, D. B., AND LONDON, E. D.: Attenuation of some signs of opioid withdrawal by inhibitors of nitric oxide synthase. Psychopharmacology 112: 521–524, 1993.
KNOWLES, R., PALACIOS, M., PALMER, R. M. J., AND MONCADA, S.: Formation of nitric oxide from L-arginine in the central nervous system. A transduction mechanism for stimulation of the soluble guanylate cyclase. Proc. Natl. Acad. Sci. USA 86: 5159–5162, 1989.
KOLESNIKOV, Y. A., PICK, C. G., CISZEWSKA, G., AND PASTERNAK, G. W.: Blockade of tolerance to morphine but not to κ-opioid by a nitric oxide synthase inhibitor. Proc. Natl. Acad. Sci. USA 90: 5162–5166, 1993.
KOLESNIKOV, Y. A., PICK, C. G., AND PASTERNAK, G. W.: N^G-nitro-L-arginine prevents morphine tolerance. Eur. J. Pharmacol. 221: 399–400, 1992.
KOOB, G. F., AND BLOOM, F. E.: Cellular and molecular mechanisms of drug dependence. Science (Wash. DC) 242: 715–723, 1988.
KOSTEN, T. R., AND KLEBER, H. D.: Buprenorphine detoxification from opioid dependence: a pilot study. Life Sci. 42: 635–641, 1988.
KOVACS, G. L., SZONTAGH, L., BALASPIRI, L., HODI, K., BOHUS, P., AND TELEGDY, G.: On the mode of action of an oxytocin derivative (Z-Pro-D-Leu) on morphine dependence in mice. Neuropharmacology 20: 647–651, 1981.
KOVACS, G. L., AND VAN REE, J. M.: Behaviorally active oxytocin fragments simultaneously attenuate heroin self-administration and tolerance in rats. Life Sci. 37: 1895–1900, 1985.
KOYUNCUOGLU, H., GUNGOR, M., EROGLU, L., AND SAGDUYU, H.: The antagonising effect of aspartic acid on morphine withdrawal and levallophan precipitated abstinence signs. Psychopharmacology 62: 89–95, 1979.
KOYUNCUOGLU, H., SAGDUYU, H., GUNGOR, M., EROGLU, L., AND GENC, E.: Antagonizing effect of aspartic acid on the development of physical dependence on and tolerance to morphine in the rat. Arzneim. Forsch. 27: 1676–1679, 1977.
KREEK, M. J.: Medical safety and side effects of methadone in tolerant subjects. J. Am. Med. Assoc. 223: 665–668, 1973.
KREEK, M. J.: Medical complications in methadone subjects. Ann. N.Y. Acad. Sci. 311: 110–134, 1978.
KREEK, M. J.: Rationale for maintenance pharmacotherapy of opioid dependence. *In* Addictive States, edited by C. P. O'Brien and J. H. Jaffe, pp. 205–230, Raven Press, New York, 1992.
KRIVOY, W. A., ZIMMERMAN, E., AND LANDE, S.: Facilitation of development of resistance to morphine analgesia by desglycinamide 9-lysine vasopressin. Proc. Natl. Acad. Sci. USA 71: 1852–1856, 1974.
KUMAR, R., STEINBERG, H., AND STOLERMAN, I. P.: Inducing a preference for morphine in rats without premedication. Nature 218: 564–565, 1968.
KUROSE, H., KATADA, T., AMANO, T., AND UI, M.: Specific uncoupling by islet-activating protein, pertussis toxin, of negative signal transduction via α-adrenergic, cholinergic and opioid receptors in neuroblastoma × glioma hybrid cells. J. Biol. Chem. 258: 4870–4875, 1983.
LAHTI, R. A., MICKELSON, M. M., MCCALL, J. M., AND VON VOIGTLANDER, P. F.: [^{3}H] U-69,593, a highly selective ligand for the opioid κ receptor. Eur. J. Pharmacol. 109: 281–284, 1985.
LAHTI, R. A., VON VOIGTLANDER, P. F., AND BARSUHN, C.: Properties of a selective kappa opioid agonist, U-50,488H. Life Sci. 31: 2257–2260, 1982.
LAKE, J. R., HAMMOND, M. V., SHADDOX, R. C., HUNSICKER, L. M., YANG, H. Y. T., AND MALIN, D. H.: IgG from neuropeptide FF antiserum reverses morphine tolerance in the rat. Neurosci. Lett. 132: 29–32, 1991.
LAL, H.: Narcotic dependence, narcotic action and dopamine receptors. Life Sci. 17: 483–496, 1975.
LAL, H., AND NUMAN, R.: Blockade of morphine withdrawal body shakes by haloperidol. Life Sci. 18: 163–168, 1976.
LEANDER, J. D., AND ORNSTEIN, P. L.: The behavioral pharmacology of LY 233536 and LY 274614: two novel, selective, competitive NMDA antagonists. Soc. Neurosci. Abstr. 16: 858, 1990.
LEE, N. M., LEVEIN, L., CHANG, J. K., AND LOH, H. H.: Opioid and peptide interaction: effect of enkephalin on morphine analgesia. Eur. J. Pharmacol. 68: 181–185, 1980.
LEWIS, J. W., RANCE, M. J., AND SANGER, D. J.: The pharmacology and abuse potential of buprenorphine: a new antagonist analgesic. Adv. Subst. Abuse 3: 103–154, 1983.
LEYBIN, L., PINSKY, C., LABELLA, F. S., HAVLICEK, V., AND REZEK, M.: Intraventricular met^5-enkephalin causes unexpected lowering of pain threshold and narcotic withdrawal signs in rats. Nature 264: 458–459, 1976.
LIGHTMAN, S. L., AND YOUNG, W. C., III: Changes in hypothalamic preproenkephalin A mRNA following stress and opiate withdrawal. Nature 328: 643–645, 1987.
LIPA, S. M., AND KAVALIERS, M.: Sex differences in the inhibitory effect of the NMDA antagonist, MK-801, on morphine and stress-induced analgesia. Brain Res. Bull. 24: 627–630, 1990.
LLORENS, C., MARTRES, M. P., BAUDRY, M., AND SCHWARTZ, J. C.: Hypersensitivity to noradrenaline in cortex after chronic morphine: relevance to tolerance and dependence. Nature 274: 603–605, 1978.
LOTSOF, H.: Rapid method for interrupting the narcotics addiction syndrome. U.S. Patent no. 4,499,096 (February 12, 1985).
LOTSOF, H.: Rapid method for interrupting cocaine and amphetamine abuse syndrome. U.S. Patent no. 4,587,243 (May 6, 1986).
LUTFY, K., HURLBUT, D., AND WEBER, E.: Blockade of morphine induced analgesia and tolerance in mice by MK-801. Brain Res. 616: 83–88, 1993.
LUX, B., AND SCHULZ, R.: Effect of cholera toxin and pertussis toxin on opioid tolerance and dependence in the guinea pig myenteric plexus. J. Pharmacol. Exp. Ther. 237: 995–1000, 1986.
MAGGIOLO, C., AND HUIDOBRO, F.: Administration of pellets of morphine to mice; abstinent syndrome. Acta Physiol. Latinoam. 11: 70–78, 1961.
MAISONNEUVE, I. M., KELLER, R. W., JR., AND GLICK, S. D.: Interactions between ibogaine, a potential anti-addictive agent, and morphine: an in vivo microdialysis study. Eur. J. Pharmacol. 199: 35–42, 1991.
MALDONADO, R., DAUGE, V., CALLEBERT, J., VILLETTE, J. M., FOURNIE-ZALUSKI, M. C., FEGER, J., AND ROQUES, B. P.: Comparison of selective and complete inhibitors of enkephalin-degrading enzymes on morphine withdrawal syndrome. Eur. J. Pharmacol. 165: 199–207, 1989.
MALDONADO, R., MICO, J. A., VALVERDE, O., SAAVEDRA, M. C., LEONSEQUI, I., AND GIBERT-RAHOLA, J.: Influence of different benzodiazepines on the experimental morphine abstinence syndrome. Psychopharmacology 105: 197–203, 1991.
MALIN, D. H., LAKE, J. R., FOWLER, D. E., HAMMOND, M. V., BROWN, S. L., LEYVA, J. E., PRASCO, P. E., AND DOUGHERTY, T. M.: FMRF-NH_2 like mammalian peptide precipitates opioid-withdrawal syndrome in the rat. Peptides 11: 277–280, 1990b.
MALIN, D. H., LAKE, J. R., HAMMOND, M. V., FOWLER, D. E., ROGILLIO, R. B., BROWN, S. L., SIMS, J. L., LEECRAFT, B. M., AND YANG, H. Y. T.: FMRF-NH_2- like mammalian octapeptide: possible role in opioid dependent and abstinence. Peptides 11: 969–972, 1990a.
MAREK, P., BEN-ELIYAHU, S., GOLD, M., AND LIEBESKIND, J. C.: Excitatory amino acid antagonists (kynurenic acid and MK-801) attenuate the development of morphine tolerance in the rat. Brain Res. 547: 77–81, 1991.
MARQUIS, K. L., PIESLA, M. J., MUTH, E. A., AND BOAST, C. A.: Effects of

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acute/chronic MK-801 on naloxone-precipitated jumping in morphine-dependent mice. Soc. Neurosci. Abstr. **17:** 331, 1991.

MARSHALL, I., AND GRAHAME-SMITH, D. G.: Evidence against a role of brain 5-hydroxytryptamine in the development of physical dependence upon morphine in mice. J. Pharmacol. Exp. Ther. **173:** 634–641, 1971.

MARTIN, B. R., DEWEY, W. L., CHAU-PHAM, T., AND PRANGE, A. J., JR.: Interactions of thyrotrophin-releasing hormone and morphine sulfate in rodents. Life Sci. **20:** 715–722, 1977.

MARTIN, W. R., AND JASINSKI, D. R.: Physiological parameters of morphine dependence in man: tolerance, early abstinence and protracted abstinence. J. Psychiatr. Res. **7:** 9–17, 1969.

MATWYSHYN, G. A., THROAT, S. N., BARJAVEL, M., GUDEHITHLU, K. P., AND BHARGAVA, H. N.: Comparative effects of MK-801 and N^G-monomethyl-L-arginine (NMMA) on morphine abstinence syndrome. Soc. Neurosci. Abstr. **19:** 1461, 1993.

MAYNERT, E. W., AND KLINGMAN, G. I.: Tolerance to morphine. I. Effects of catecholamines in brain and adrenal glands. J. Pharmacol. Exp. Ther. **135:** 285–296, 1962.

MEISHERI, K. D., AND ISOM, G. E.: Influence of immune stimulation and suppression on morphine physical dependence and tolerance. Res. Commun. Chem. Pathol. Pharmacol. **19:** 85–99, 1978.

MELLO, N. K., MENDELSON, J. H., AND KUEHNLE, J. C.: Buprenorphine effects on human self-administration. J. Pharmacol. Exp. Ther. **223:** 30–39, 1982.

MITTELMAN, A., KROWN, S. E., CIRRINCIONE, C., SAFAI, B., OETTGEN, H. F., AND KOZINER, B.: Analysis of T cell subsets in cancer patients treated with interferon. Am. J. Med. **75:** 966–972, 1983.

MONAGHAN, D. T., BRIDGES, R. J., AND COTMAN, C. W.: The excitatory aminoacid receptors: their classes, pharmacology and distinct properties in the function of the central nervous system. Annu. Rev. Pharmacol. Toxicol. **29:** 365–402, 1989.

MORLEY, J. E., YAMADA, T., WALSH, J. H., LAMERS, H., WONG, H., SHULKES, A., DAMASSA, D. A., GORDON, J., CARLSON, H. E., AND HERSHMAN, J. M.: Morphine addiction and withdrawal alters brain peptide concentrations. Life Sci. **26:** 2239–2244, 1980.

MUSHLIN, B. E., AND COCHIN, J.: Tolerance to morphine in the rat: its prevention by naloxone. Life Sci. **18:** 797–802, 1976.

NATHENSON, G., GOLDEN, G. S., AND LITT, I. P.: Diazepam in the management of the neonatal narcotic withdrawal syndrome. Pediatrics **48:** 523–527, 1971.

NEAL, B. S., AND SPARBER, S. B.: Mianserine attenuates naloxone-precipitated withdrawal signs in rats acutely or chronically dependent upon morphine. J. Pharmacol. Exp. Ther. **236:** 157–165, 1986.

NORTH, R. A.: Opioid receptor types and membrane ion channels. Trends Neurosci. **9:** 114–117, 1986.

NUMAN, R., SMITH, N., AND LAL, H.: A versatile procedure for rapid induction of narcotic addiction in the rat utilizing intravenous injections. Physiol. Psychol. **3:** 261–262, 1975.

O'BRIEN, C. P., TERENIUS, L., NYBERG, F., MCLELLAN, A. T., AND ERIKSSON, I.: Endogenous opioid in cerebrospinal fluid of opioid-dependent subjects. Biol. Psychiatry **24:** 649–662, 1988.

O'DOWD, B. F.: Structures of dopamine receptors. J. Neurochem. **60:** 804–816, 1993.

OHNISHI, T., SAITO, K., MATSUMOTO, K., SAKUDA, M., AND INOKI, R.: Decrease in analgesic effect of nifedipine following chronic morphine administration. Eur. J. Pharmacol. **158:** 173–175, 1988.

OHNISHI, T., SAITO, K., MATSUMOTO, K., SAKUDA, M., ISHII, K., AND INOKI, R.: Changes in [^{3}H] nitrendipine binding and γ-aminobutyric acid release in rat hippocampus following repeated morphine administration. J. Neurochem. **53:** 1507–1511, 1989.

OKA, T., NEGISHI, K., KAJIWARA, M., WATANABE, Y., ISHIZUKA, Y., AND MATSUMIYA, T.: The choice of opioid receptor subtype by neoendorphins. Eur. J. Pharmacol. **79:** 301–305, 1982.

O'NEILL, M. F., DOURISH, C. T., AND IVERSEN, S. D.: Morphine-induced analgesia in the rat paw pressure test is blocked by CCK and enhanced by the CCK antagonist MK-329. Neuropharmacology **28:** 243–247, 1989.

ORAHOVATS, P. D., WINTER, C. A., AND LEHMAN, E. G.: The effect of N-alkylnormorphine upon the development of tolerance to morphine in the albino rat. J. Pharmacol. Exp. Ther. **109:** 413–416, 1953.

ORNSTEIN, P. L., ARNOLD, M. B., AUGENSTEIN, N. K., SCHOEPP, D. D., LEANDER, J. D., AND LODGE, D.: The discovery of LY 274614 and LY 233536 and their characterization as selective and competitive NMDA antagonists. Soc. Neurosci. Abstr. **16:** 858, 1990.

PANERAI, A. E., ROVATI, L. C., COCCO, E., SACERDOTE, P., AND MANTEGAZZA, P.: Dissociation of tolerance and dependence to morphine: a possible role for cholecystokin. Brain Res. **410:** 52–60, 1987.

PARENTI, M., TIRONE, F., GIAGNONI, G., PECORA, N., AND PAROLARO, D.: Pertussis toxin inhibits the antinociceptive action of morphine in the rat. Eur. J. Pharmacol. **124:** 357–359, 1986.

PAROLARO, D., PATRINI, G., GIAGNONI, G., MASSI, P., GROPPETTI, A., AND PARENTI, M.: Pertussis toxin inhibits morphine analgesia and prevents opioid dependence. Pharmacol. Biochem. Behav. **35:** 137–141, 1990.

PASTERNAK, G. W., SIMANTOV, R., AND SNYDER, S. H.: Characterization of an endogenous morphine-like factor (enkephalin) in mammalian brain. Mol. Pharmacol. **12:** 504–513, 1976.

PECILE, A., FERRI, S., BRAGA, P. C., AND OLGIATI, V. R.: Effects of intracerebroventricular calcitonin in the conscious rabbit. Experientia **31:** 332–333, 1975.

PFAFFINGER, P. J., MARTIN, J. M., HUNTER, D. D., NATHANSON, N. M., AND HILLE, B.: GTP-binding proteins couple cardiac muscarinic receptors to a K^+-channel. Nature **317:** 536–538, 1985.

PINSKY, C., DUA, A. K., AND LABELLA, F. S.: Peptidase inhibitors reduce opioid narcotic withdrawal signs, including seizure activity, in the rat. Brain Res. **243:** 301–307, 1982.

PINSKY, C., FREDERICKSON, R. C. A., AND VAZQUEZ, A. J.: Morphine withdrawal syndrome responses to cholinergic antagonists and to a partial cholinergic agonist. Nature **242:** 59–60, 1973.

PLOTNIKOFF, N. P., PRANGE, A. J., BREESE, G. R., AND ERSON, M. S., AND WILSON, I. C.: Enhancement of dopa activity by a hypothalamic hormone. Science (Wash. DC) **178:** 417–418, 1972.

PLOTNIKOFF, N. P., PRANGE, A. J., BREESE, G. R., AND WILSON, I. C.: Thyrotropin-releasing hormone: enhancement of dopa activity in thyroidectomized rats. Life Sci. **14:** 1271–1278, 1974.

PRICE, D. A., AND GREENBERG, M. J.: The structure of molluscan cardioexcitatory neuropeptide. Science (Wash. DC) **197:** 670–671, 1977.

PRZEWLOCI, R., COSTA, T., LANG, J., AND HERZ, A.: Pertussis toxin abolishes the antinociception mediated by opioid receptors in the rat spinal cord. Eur. J. Pharmacol. **144:** 91–95, 1987.

PRZEWLOCI, R., HOLT, V., DUKA, T. H., KLEBER, G., GRAMSCH, C. H., HAARMAAN, I., AND HERZ, A.: Long-term morphine treatment decreases endorphin levels in rat brain and pituitary. Brain Res. **174:** 357–361, 1979.

PURI, S. K., AND LAL, H.: Effect of dopaminergic stimulation or blockade on morphine withdrawal aggression. Psychopharmacology **32:** 113–120, 1973.

RAHMANI, N. H, GULATI, A., AND BHARGAVA, H. N.: Spinal cord receptors for thyrotropin releasing hormone of morphine tolerant-dependent and abstinent rats. Peptides **11:** 693–695, 1990.

RAMARAO, P., AND BHARGAVA, H. N.: Effect of thyrotrophin releasing hormone on the development of tolerance to the analgesic and hyperthermic effects of morphine in the rat. Neuropeptides **15:** 213–217, 1990a.

RAMARAO, P., AND BHARGAVA, H. N.: Antagonism of the acute pharmacological actions of morphine by Panax ginseng extract. Gen. Pharmacol. **21:** 877–880, 1990b.

RAMARAO, P., JABLONSKI, H. I., JR., REHDER, K. R., AND BHARGAVA, H. N.: Effect of κ-opioid receptor agonists on morphine analgesia in morphine-naive and morphine-tolerant rats. Eur. J. Pharmacol. **156:** 239–246, 1988.

RAMKUMAR, V., AND EL-FAKAHANY, E. E.: Increase in ^{3}H-nitrendipine binding sites in morphine tolerant mice. Eur. J. Pharmacol. **102:** 371–372, 1984.

RAMKUMAR, V., AND EL-FAKAHANY, E. E.: Prolonged morphine treatment increases rat brain dihydropyridine binding sites, possible involvement in development of morphine dependence. Eur. J. Pharmacol. **146:** 73–83, 1988.

RASMUSSEN, K., FULLER, R. W., STOCKTON, M. E., PERRY, K. W., SWINFORD, R. M., AND ORNSTEIN, P. L.: NMDA receptor antagonists suppress behaviors but not norepinephrine turnover or locus coeruleus unit activity induced by opioid withdrawal. Eur. J. Pharmacol. **197:** 9–16, 1991.

RASMUSSEN, L., AND MERIGAN, T. C.: Effect of interferon therapy on circulating lymphocytes in humans. J. Interferon Res. **1:** 102–110, 1980.

RATTAN, A. K., KOO, K. L., TEJWANI, G. A., AND BHARGAVA, H. N.: The effect of morphine tolerance dependence and abstinence on immunoreactive dynorphin (1–13) levels in discrete brain regions, spinal cord, pituitary gland and peripheral tissues of the rat. Brain Res. **584:** 207–212, 1992.

REDDY, P. L., VEERANNA, THORAT, S. N., AND BHARGAVA, H. N.: Evidence for the supersensitivity of dopamine D_2 receptors without receptor up-regulation in morphine abstinent rats. Brain Res. **607:** 293–300, 1993.

REDMOND, D. E., AND HUANG, Y. H.: The primate locus coeruleus and effects of clonidine on opioid withdrawal. J. Clin. Psychiatry **43:** 25–29, 1982.

REISINGER, M.: Buprenorphine as a new treatment for heroin dependence. Drug Alcohol Depend. **16:** 257–252, 1985.

RESNICK, R. B., GALANTER, M., PYCHA, C., COHEN, A., GRANDISON, P., AND FLOOD, N.: Buprenorphine: an alternate to methadone for heroin dependence treatment. Psychopharmacol. Bull. **28:** 109–113, 1992.

RESNICK, R. B., KESTENBAUM, R. S., WASHTON, A., AND POOLE, D.: Naloxone-precipiated withdrawal: a method for rapid induction on to naltrexone. Clin. Pharmacol. Ther. **21:** 409–413, 1977.

RESNICK, R. B., RESNICK, E., AND GALANTER, M.: Buprenorphine responders: a diagnostic subgroup of heroin addicts. Prog. Neuro-psychopharmacol. Biol. Psychiatry **15:** 531–538, 1991.

REZVANI, A., AND WAY, E. L.: Dynorphin (1–13) restores the potency of morphine on tolerant guinea pig ileum. Eur. J. Pharmacol. **102:** 475–479, 1984.

RITZMANN, R. F., WALTER, R., BHARGAVA, H. N., AND FLEXNER, L. B.: Blockage of narcotic induced dopamine receptor supersensitivity by cyclo (Leu-Gly). Proc. Natl. Acad. Sci. USA **76:** 5997–5998, 1979.

ROMER, D., BUSCHER, H. H., HILL, R. C., MAURER, R., PETCHER, T. J., WELLE, H. B. A., BAKEL, H. C. C. K., AND AKKERMANN, A. M.: Bremazocine: a potent, long-acting opioid kappa agonist. Life Sci. **27:** 971–978, 1980.

ROQUES, B. P., NOBLE, F., DAUGE, V., FOURNIE-ZALUSKI, M. C., AND BEAUMONT, A.: Neutral endopeptidase 24.11: structure, inhibition, and experimental and clinical pharmacology. Pharmacol. Rev. **45:** 87–146, 1993.

ROSS, D. H.: Calcium contents and binding in synaptosomal subfractions during chronic morphine treatment. Neurochem. Res. **2:** 581–593, 1977.

ROTHMAN, R. B., LONG, J. B., BYKOV, V., XU, H., JACOBSON, A. E., RICE, K. C., AND HOLADAY, J. W.: Up-regulation of the opioid receptor complex by the

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chronic administration of morphine: a biochemical marker related to the development of tolerance and dependence. Peptides 12: 151–160, 1991.

RUIZ-GAYO, M., DURIEUX, C., FOURNIE-ZALUSKI, M. C., AND ROQUES, B. P.: Stimulation of δ-opioid receptors reduces the in vivo binding of the cholecystokinin (CCK)-B-selective agonist [^{3}H]pBC 264: evidence for a physiological regulation of CCK-ergic system by endogenous enkephalins. J. Neurochem. 59: 1805–1811, 1992.

SAITO, K., ISHII, K., FUJITA, N., NAKAHIRO, M., AND INOKI, R.: Selective enhancement in striatal ^{3}H-nitrendipine binding following chronic treatment with morphine. Neurochem. Int. 6: 1033–1036, 1985.

SAMANIN, R., CERVO, L., AND ROCHAT, C.: Changes of physical morphine dependence in rats chronically treated with drugs acting on brain 5-hydroxytryptamine. J. Pharm. Pharmacol. 32: 150, 1980a.

SAMANIN, R., CERVO, L., ROCHAT, C., POGGESI, E., AND MENNINI, T.: Reduction in the number of serotonin receptors in the brain stem of morphine dependent rats: relation to blockade of naloxone-precipitated jumping by serotonin agonists. Life Sci. 27: 1141–1146, 1980b.

SANGHVI, I. S., AND GERSHON, S.: Morphine dependent rats: blockade of precipitated abstinence by calcium. Life Sci. 18: 649–654, 1977.

SCHMAUSS, C., AND HERZ, A.: Intrathecally administered dynorphin (1–17) modulates morphine-induced antinociception differently in morphine-naive and morphine-tolerant rats. Eur. J. Pharmacol. 135: 429–431, 1987.

SCHMIDT, H. H. H. W., WIKE, P., EVERS, B., AND BOHME, E.: Enzymatic formation of nitrogen oxide from L-arginine in bovine brain cytosol. Biochem. Biophys. Res. Commun. 165: 284–291, 1989.

SCHNEIDER, J. A., AND MCARTHUR, M.: Potentiation action of ibogaine (Bogadin TM) on morphine analgesia. Experientia 12: 323–324, 1956.

SCHOEPP, D. D., ORNSTEIN, P. L., SALHOFF, C. R., AND LEANDER, J. D.: Neuroprotectant effects of LY 274614, a structurally novel systemically active competitive NMDA receptor antagonist. J. Neural Transm. 85: 133–143, 1991.

SCHREIER, W. A., AND BURKS, T. F.: Suppression of morphine withdrawal diarrhea by clonidine. Proc. West. Pharmacol. Soc. 24: 341–345, 1981.

SCHUSTER, C. R., AND THOMPSON, T.: Self-administration of and behavioral dependence on drugs. Annu. Rev. Pharmacol. Toxicol. 9: 483–502, 1969.

SCHWARTZ, J. C.: Metabolism of enkephalins and the inactivating neuropeptidase concept. Trends Neurosci. 6: 45–48, 1983.

SEEVERS, M. H., AND DENEAU, G. A.: Physiological aspects of tolerance and physical dependence. *In* Physiological Pharmacology, edited by W. S. Root and F. G. Hofmann, Vol. 1, pp. 565–640, Academic Press, New York, 1963.

SETHY, V. H., AND VAN WOERT, M. H.: Modification of striatal acetylcholine concentration by dopamine receptor agonists and antagonists. Res. Commun. Chem. Path. Pharmacol. 8: 13–28, 1974.

SHARMA, S. K., KLEE, W. A., AND NIRENBERG, M.: Dual regulation of adenylate cyclase accounts for narcotic dependence and tolerance. Proc. Natl. Acad. Sci. USA 72: 3092–3096, 1975.

SHARMA, S. K., KLEE, W. A., AND NIRENBERG, M.: Opioid-dependent modulation of adenylate cyclase. Proc. Natl. Acad. Sci. USA 74: 3365–3369, 1977.

SHARPE, L. G., AND JAFFE, J. H.: Ibogaine fails to reduce naloxone-precipitated withdrawal in the morphine-dependent rat. Neuroreport 1: 5–7, 1990.

SHEARMAN, G. T., LAL, H., AND URSILLO, R. C.: Effectiveness of lofexidine in blocking morphine-withdrawal signs in the rat. Pharmacol. Biochem. Behav. 12: 573–575, 1980.

SMITH, C. B., HOLLINGSWORTH, P. J., GEER, J. J., AND MOISES, H. C.: Changes in α_2-adrenoreceptors in various areas of the rat brain after long-term administration of "mu" and "kappa" opioid agonists. Life Sci. 33: 369–372, 1983.

SMITH, E. M., AND BLALOCK, J. E.: Human lymphocyte production of corticotropin and endorphin-like substances: association with leukocyte interferon. Proc. Natl. Acad. Sci. USA 78: 7530–7534, 1981.

SMITS, E. E.: Antagonism by naloxone of morphine-induced single-dose dependence and antinociception in mice. Res. Commun. Chem. Path. Pharmacol. 15: 689–696, 1976.

SPARBER, S. B., AND MEYER, D. R.: Clonidine antagonizes naloxone-induced suppression of conditioned behavior and body weight loss in morphine-dependent rats. Pharmacol. Biochem. Behav. 9: 319–325, 1978.

STADLER, H., LLOYD, K. G., GADE-CIRIA, M., AND BARTHOLINI, G.: Enhanced striatal acetylcholine release by chlorpromazine and its reversal by apomorphine. Brain Res. 55: 476–480, 1973.

SUGERMAN, A. A., MIKSTAL, M. W., AND FREYMUTH, H. W.: Comparison of prazepam and placebo in the treatment of convalescing narcotic addict. J. Clin. Pharmacol. 11: 383–387, 1971.

SWAIN, H. H., AND SEEVERS, M. H.: Evaluation of new compounds for morphine-like physical dependence in the rhesus monkey. Bull. Prob. Drug Depend. 36 (addendum 1): 168, 1974.

SWAIN, H. H., AND SEEVERS, M. H.: Evaluation of new compounds for morphine-like physical dependence in the rhesus monkey. Bull. Prob. Drug Depend. 36 (addendum 2): 768, 1976.

TAGLIARO, F., DORIZZI, R., LAFISCA, S., MASCHIO, S., AND MARIGO, M.: Calcitonin serum levels in heroin addicts: effects of methadone and clonidine detoxification treatment. Drug. Alcohol Depend. 16: 181–183, 1985.

TAKAHASHI, M., SENDA, T. J., AND KANETO, H.: Role of spinal k-opioid receptors in the blockade of the development of antinociceptive tolerance to morphine. Eur. J. Pharmacol. 200: 293–297, 1991.

TAKEMORI, A. E., LOH, H. H., AND LEE, N. M.: Suppression by dynorphin A (1–13) of the expression of opioid withdrawal and tolerance in mice. Eur. J. Pharmacol. 221: 223–226, 1992.

TAKEMORI, A. E., LOH, H. H., AND LEE, N. M.: Suppression by dynorphin A and [Des-Tyr^1] dynorphin A peptides of the expression of opiate withdrawal and tolerance in morphine-dependent mice. J. Pharmacol. Exp. Ther. 266: 121–124, 1993.

TANG, J., CHOU, J., IADAROLA, M., YANG, H. Y. T., AND COSTA, E.: Proglumide prevents and curtails acute tolerance to morphine in rats. Neuropharmacology 23: 715–718, 1984a.

TANG, J., YANG, H. Y. T., AND COSTA, E.: Inhibition of spontaneous and opioid modified nociception by an endogenous neuropeptide with Phe-Met-Arg-Phe-NH_2-like immunoreactivity. Proc. Natl. Acad. Sci. USA 81: 5002–5005, 1984b.

TAO, P. L., AND LIU, C. F.: Chronic morphine treatment causes down-regulation of spinal A_1 receptors in rats. Eur. J. Pharmacol. 215: 301–304, 1992.

TEJWANI, G. A., RATTAN, A. K., KOO, K. L., MATWYSHYN, G. A., AND BHARGAVA, H. N.: Methionine-enkephalin concentrations in discrete brain regions, spinal cord, pituitary gland and peripheral tissues of U-50,488H tolerant and abstinent rats. Pharmacology 48: 216–225, 1994.

TEJWANI, G. A., RATTAN, A. K., SRIBANDITMONGKOL, P., SHEU, M. J., ZUNIGA, J., AND MCDONALD, J. S.: Inhibition of morphine-induced tolerance and dependence by a benzodiazepine receptor agonist midazolam in the rat. Anesth. Analg. 76: 1052–1060, 1993.

THORAT, S. N., BARJAVEL, M., MATWYSHYN, G. A., AND BHARGAVA, H. N.: Comparative effects of N^G-monomethyl-L-arginine and MK-801 on the abstinence syndrome in morphine-dependent mice. Brain Res., 642: 153–159, 1994.

THORAT, S. N., AND BHARGAVA, H. N.: Evidence for the cross-tolerance between morphine and Δ^9-tetrahydrocannabinol in mice. Eur. J. Pharmacol., 260: 5–13, 1994.

THORAT, S. N., REDDY, P. L., AND BHARGAVA, H. N.: Evidence for the role of nitric oxide in κ-opioid tolerance in mice. Brain Res. 621: 171–174, 1993a.

THORAT, S. N., VEERANNA, REDDY, P. L., AND BHARGAVA, H. N.: Biochemical and behavioral studies on the interaction between μ- and κ-opiate agonist in mice. Brain Res. 615: 191–198, 1993b.

TICKU, M. K., AND HUFFMAN, R. D.: The effects of acute and chronic morphine administration on GABA receptor binding. Eur. J. Pharmacol. 68: 97–106, 1980.

TISEO, P. J., AND INTURRISI, C. E.: Attenuation and reversal of morphine tolerance by the competitive N-methyl-D-aspartate receptor antagonist, LY 274614. J. Pharmacol. Exp. Ther. 264: 1090–1096, 1993.

TREMBLAY, E., COLOMBEL, M. C., AND JACOB, J.: Précipitation et prévention de l'abstinence chez le rat et la souris en état de dépendence aigue: comparison de la diprenorphine. Psychopharmacology 49: 41–48, 1976.

TRUJILLO, K. A., AND AKIL, H.: Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. Science (Wash. DC) 251: 85–87, 1991.

TSENG, L. F., LOH, H. H., AND LI, C. H.: β-Endorphin: cross-tolerance to and cross-dependence on morphine. Proc. Natl. Acad. Sci. USA 37: 4187–4189, 1976.

TSENG, L. F., LOH, H. H., AND WEI, E. T.: Effects of clonidine on morphine withdrawal signs in the rat. Eur. J. Pharmacol. 30: 93–99, 1975.

TUCKER, J. F.: Effect of pertussis toxin on normorphine dependence and on acute inhibitory effects of normorphine and clonidine in guinea pig isolated ileum. Br. J. Pharmacol. 83: 326–328, 1984.

TULUNAY, F. C., JEN, M. F., CHANG, J. K., LOH, H. H., AND LEE, N. M.: Possible regulatory role of dynorphin on morphine and β-endorphin induced analgesia. J. Pharmacol. Exp. Ther. 219: 296–298, 1981.

UHL, G. R., RYAN, J. P., AND SCHWARTZ, J. P.: Morphine alters preproenkephalin gene expression. Brain Res. 459: 391–397, 1988.

VALVERDE, O., MICO, J. A., MALDONADO, R., AND GIBERT-RAHOLA, J.: Changes in benzodiazepine-receptor activity modify morphine withdrawal syndrome in mice. Drug Alcohol Depend. 30: 293–300, 1992.

VAN CALKER, D., MULLER, M., AND HAMPRECHT, B.: Adenosine regulates via two different types of receptors, the accumulation of cyclic AMP in cultured brain cells. J. Neurochem. 33: 999–1005, 1979.

VAN REE, J. M., AND DE WIED, D.: Prolyl-leucyl-glycinamide (PLG) facilitates morphine dependence. Life Sci. 19: 1331–1340, 1976.

VAUGHT, J. L., AND TAKEMORI, A. E.: Differential effects of leucine and methionine-enkephalin on morphine-induced analgesia, acute tolerance, and dependence. J. Pharmacol. Exp. Ther. 208: 86–90, 1979.

VEERANNA, REDDY, P. L., AND BHARGAVA, H. N.: Abstinence from U-50,488H, a κ-opiate agonist, decreases the binding of ^{3}H-DPAT to 5-HT_{1A} receptors in the hypothalamus of the rat. Neuropharmacology 31: 1243–1249, 1992.

VEERANNA, REDDY, P. L., AND BHARGAVA, H. N.: Effect of chronic administration of U-50,488H, a kappa opiate receptor agonist, on central dopamine D_2 receptors in the rat. Eur. J. Pharmacol. 235: 23–30, 1993.

VENTAFRIDDA, V., FIGLIUZZI, M., TAMBURINI, M., GORI, E., PARCLARO, D., AND SALA, M.: Clinical observations on analgesia elicited by intrathecal morphine in cancer patients. *In* Advances in Pain Research and Therapy, edited by J. J. Bonica, Vol. 3, pp. 559–565, Raven Press, New York, 1979.

VETULANI, J., AND BEDNARCZYK, B.: Depression by clonidine of shaking behavior elicitated by nalorphine in morphine dependent rats. J. Pharm. Pharmacol. 29: 567–569, 1977.

VILCEK, J., NG, M. H., FRIEDMAN-KIEN, A. E., AND KRAWEIW, T.: Induction of interferon synthesis by synthetic double-stranded polynucleotides. J. Virol. 2: 648–650, 1968.

VILLAREAL, J. E., AND SEEVERS, M. H.: Evaluation of new compounds for

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morphine-like physical dependence in the rhesus monkey. Bull. Prob. Drug Depend. 34 (addendum 7): 1040, 1972.
VOLPE, A., FACCHINETTI, F., CIONI, A., AND GENAZZONI, A. R.: Reduction of β-endorphin levels in the amniotic fluid of heroin addicts. Obstet. Gynecol. 68: 606–609, 1986.
VON VOIGTLANDER, P. F., LAHTI, R. A., AND LUDENS, J. H.: U-50,488H: a selective and structurally novel non-mu (kappa) opioid agonist. J. Pharmacol. Exp. Ther. 224: 7–14, 1983.
VON VOIGTLANDER, P. F., AND LEWIS, R. A.: Analgesic and mechanistic evaluation of spiradoline, a potent kappa opioid. J. Pharmacol. Exp. Ther. 246: 259–262, 1988.
WALKER, J. M., MOISES, H. C., COY, D. H., BALDRIGHT, G., AND AKIL, H.: Non-opiate effects of dynorphin and des-Tyr-dynorphin. Science (Wash. DC) 218: 1136–1138, 1982.
WALTER, R., RITZMANN, R. F., BHARGAVA, H. N., AND FLEXNER, L. B.: Prolyl-leucyl-glycinesamide, cyclo (leucylglycine) and derivatives block development of physical dependence on morphine in mice. Proc. Natl. Acad. Sci. USA 76: 518–520, 1979.
WALTER, R., RITZMANN, R. F., BHARGAVA, H. N., RAINBOW, T. C., FLEXNER, L. B., AND KRIVOY, W. A.: Inhibition by Z-Pro-D-Leu of development of tolerance to and physical dependence on morphine in mice. Proc. Natl. Acad. Sci. USA 75: 4573–4576, 1978.
WANG, J. K., NAUSS, L. A., AND THOMAS, J. E.: Pain relief by intrathecally applied morphine in man. Anesthesiology 50: 149–151, 1979.
WARD, S. J., PORTOGHESE, P. S., AND TAKEMORI, A. E.: Pharmacological characterization in vivo of the novel opioid, β-funaltrexamine. J. Pharmacol. Exp. Ther. 220: 494–498, 1982.
WATKINS, L., KINSCHECK, I. B., AND MAYER, D. J.: Potentiation of morphine analgesia and apparent reversal of morphine tolerance by proglumide. Science (Wash. DC) 224: 395–396, 1984.
WAY, E. L., LOH, H. H., AND SHEN, F. H.: Morphine tolerance, physical dependence, and synthesis of brain 5-hydroxytryptamine. Science (Wash. DC) 162: 1290–1292, 1968.
WAY, E. L., LOH, H. H., AND SHEN, F. H.: Simultaneous quantitative assessment of morphine tolerance and physical dependence. J. Pharmacol. Exp. Ther. 167: 1–8, 1969.
WEBER, E., EVANS, C. J., SAMUELSSON, S. J., AND BARCHAS, J. D.: Novel peptide neuronal system in rat brain and pituitary. Science (Wash. DC) 214: 1248–1251, 1981.
WEEKS, J. R.: Experimental morphine addiction: method for automatic intravenous injections in unrestrained rats. Science (Wash. DC) 138: 143–144, 1962.
WEEKS, J. R., AND COLLINS, R. J.: Dose and physical dependence as factors in the self-administration of morphine by rats. Psychopharmacology 65: 171–177, 1979.
WEI, E., AND LOH, H. H.: Physical dependence on opioid-like peptides. Science (Wash. DC) 193: 1262–1263, 1976.
WEI, E., LOH, H. H., AND WAY, E. L.: Quantitative aspects of precipitated abstinence in morphine dependent rats. J. Pharmacol. Exp. Ther. 185: 108–115, 1973.
WEINSTEIN, Y., BRODEUS, B. R., MELMON, K. L., AND MERIGAN, T. C.: Interferon inhibition of lymphocyte mitogenesis. Immunobiology 33: 313–319, 1977.
WEN, H. L., AND HO, W. K. K.: Suppression of withdrawal symptoms by dynorphin in heroin addicts. Eur. J. Pharmacol. 82: 183–186, 1982.
WEN, H. L., HO, W. K. K., AND WEN, P. Y. C.: Comparison of the effectiveness of different opioid peptides in suppressing heroin withdrawal. Eur. J. Pharmacol. 100: 155–162, 1984.
WERLING, L. L., MCMAHON, P. N., AND COX, B. M.: Selective changes in μ-opioid receptor properties induced by chronic morphine exposure. Proc. Natl. Acad. Sci. USA 86: 6393–6397, 1989.
WESCHE, D., HOLLT, V., AND HERZ, A.: Radioimmunoassays of enkephalins. Regional distribution in rat brain after morphine treatment and hypophysectomy. Naunyn Schmiedebergs Arch. Exp. Pathol. Pharmakol. 301: 79–82, 1977.
WIESENFELD-HALLIN, Z., AND DURANTI, R.: Intrathecal cholecystokinin interacts with morphine but not substance P in modulating the nociceptive flexion reflex in the rat. Peptides 8: 153–158, 1987.
WILLETTS, J., BALSTER, R. L., AND LEANDER, J. D.: The behavioral pharmacology of NMDA receptor antagonists. Trends Pharmacol. Sci. 11: 423–428, 1990.
WISE, R. A., AND BOZARTH, M. A.: Action of drugs of abuse on brain reward system: an update with specific attention to opioid. Pharmacol. Biochem. Behav. 17: 239–243, 1982.
WONG, E. H. F., KNIGHT, A. R., AND WOODRUFF, G. N.: [^{3}H]MK-801 labels a site on the N-methyl-D-asparate receptor channel complex in rat brain membranes. J. Neurochem. 50: 274–281, 1988.
YAMAMOTO, H., HARRIS, R. A., LOH, H. H., AND WAY, E. L.: Effects of acute and chronic morphine treatment on calcium localization and binding in brain. J. Pharmacol. Exp. Ther. 205: 255–264, 1978.
YAMAMOTO, M., KUMAGAI, F., TACHIKAWA, S., AND MAENO, H.: Lack of effect of levallorphan on analgesia induced by intraventricular application of porcine calcitonin in mice. Eur. J. Pharmacol. 55: 211–213, 1979.
YAMAMOTO, T., OHNO, M., AND VEKI, S.: A selective κ-opioid agonist, U-50,488H, blocks the development of tolerance to morphine analgesia in rats. Eur. J. Pharmacol. 156: 173–176, 1988.
YANAURA, S., AND SUZUKI, T.: Preference for morphine and drug seeking behavior in morphine dependent rats. Jpn. J. Pharmacol. 28: 707–717, 1978.
YANAURA, S., UESUGI, J., SUZUKI, T., AND KAWAI, T.: Oral self-administration of morphine in rats. Jpn. J. Pharmacol. 30: 258–261, 1980.
YANG, H. Y. T., FRATTA, W., MAJANE, E. A., AND COSTA, E.: Isolation, sequencing, synthesis, and pharmacological characterization of two brain neuropeptides that modulate the action of morphine. Proc. Natl. Acad. Sci. USA 82: 7757–7761, 1985.
YANO, I., AND TAKEMORI, A. E.: Inhibition by naloxone of tolerance and dependence in mice treated acutely and chronically with morphine. Res. Commun. Chem. Pathol. Pharmacol. 16: 721–734, 1977.
YATANI, A., CODINA, J., BROWN, A. M., AND BIRNBAUMER, L.: Direct activation of mammalian atrial muscarinic potassium channels by GTP regulatory G_k. Science (Wash. DC) 235: 207–211, 1987.
YOUNG, G. A., STEINFELS, G. F., AND KHAZAN, N.: Spontaneous vs. naloxone-induced abstinence in dependent rats self-administering L-alpha acetylmethadol (LAAM) or morphine. Pharmacol. Biochem. Behav. 10: 585–589, 1979.

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