

# Chapter 2

## The Evolution of Concepts

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**Abstract**  $\kappa$  Opioid receptors were first proposed by the author based on the actions of benzomorphans, such as ketocyclazocine.  $\kappa$  receptors are involved with a wide range of actions, providing novel targets for drug development. This chapter will explore the pharmacology of  $\kappa$  receptors in a range of behavioral effects and their functions at the biological level.

**Keywords**  $\kappa$  Receptor • KOR • Electrophysiology • Dynorpin • Epilepsy • Stress • Depression • Learning • LTP • DRG • Ion channel • Kinase

### 2.1 Introduction

The early evolution of concepts of endogenous opioids and multiple receptors had its inception in a concerted program to develop safe, nonaddicting substitutes for opiates [1]. This endeavor was initiated but the Bureau of Social Hygiene and subsequently supported by the US Public Health Service under the auspices of the National Research Council. An empiric approach was taken in which a large number of chemicals, synthesized by University-based chemists and the pharmaceutical industry, were examined for their pharmacologic effects, particularly their analgesic activity and their abuse potential.

Although heroin and morphine addiction were the initial driving force of this endeavor, the economic gains associated with the marketing of a less-addicting analgesic became the most important factor of the pharmaceutical industry's synthetic effort. From a societal perspective, however, the economics of drug abuse is by far the most important economic factor, since drug abuse costs the United States well over \$100 billion dollars a year. The search for safer and less-abusable

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analgesics has not been entirely successful. The evolution of ideas concerning multiple opioid receptors and endogenous opioid transmitters is still active.

The critical opioids in the pharmacologic dissection of multiple opioid receptors were *N*-allylnorcodeine, *N*-allylnormorphine, naloxone, cyclazocine, ethylketazocine, *N*-allylnormetazocine, and buprenorphine. Proceeding on the concept that allyl substitutions functioned as respiratory stimulants, Von Braun [2] synthesized *N*-allylnorcodeine and Pohl [3] studied the interactions between *N*-allylnorcodeine and morphine and first demonstrated that *N*-allylnorcodeine was capable of antagonizing the respiratory depressant effects of morphine.

Although Pohl's important observations were published in 1915 and were confirmed by Meissner [4], these findings lay dormant until they were resurrected again by Chauncy Leake. Dr. Leake, then of the University of California in San Francisco, stimulated efforts to synthesize *N*-allylnorcodeine and allylnormorphine. These endeavors have been briefly recounted [5], and, like Pohl's concept, were based on the hypothesis that allyl groups are respiratory stimulants.

The initial synthesis of *N*-allylnormorphine was controversial. As a consequence of resolving the synthetic issues, *N*-allylnormorphine (nalorphine) was independently synthesized by Weijlard and Erickson at Merck Laboratories [6] and by Hart and McCauley at the University of California [7]. Both Unna [8] and Hart and McCauley [7] also studied the pharmacology of this interesting compound and extended the observations of Pohl by showing that nalorphine antagonized other actions of morphine.

The issue of respiratory stimulant action can be clearly differentiated from its morphine antagonistic effect and from the respiratory stimulant actions of dinitrophenol. The observations of nalorphine's antagonistic effects were reluctantly accepted, as were speculations concerning its mechanism of action (Unna, personal communication). The clinical use of nalorphine for the treatment of acute morphinism was not pursued despite Unna's urging and was not demonstrated until Eckenhoff et al. [9] conducted the critical experiment in man.

To further elaborate on the importance of opiate addiction in stimulating research on opioid drugs, a Committee on Drug Addiction was formed by the Committee on Social Hygiene in 1920 to increase the understanding of addiction processes. Following the passage of the Harrison Narcotic Act and on the recommendation of the American Medical Association, clinics that provided narcotics to addicts were closed, leaving most addicts without a legitimate source for their narcotics. As part of the Committee's activities, they proposed a strategy for identifying new analgesics that would be devoid of the toxic and dependence-producing actions of the opium analgesics. Subsequently, the Federal government assumed the responsibility of continuing the activities of this committee.

Among the important activities were the initiation and continuation of a synthetic program, the development of an animal screening program, and finally assessment of new analgesics in humans for their ability to produce or sustain physical dependence. Many compounds were synthesized and evaluated by Dr. Eddy's laboratory at the National Institutes of Health, by Dr. Severs' laboratory at the University of Michigan, and by investigators of human subjects at the Addiction Research Center.

Most of the drugs studied were sufficiently like morphine that they were judged not to have any marked advantage. In retrospect, there may have been significant differences between the drugs; these were either not detected using the methods at hand, or differences were not pursued. Two examples of compounds that had unique pharmacological properties in human subjects were meperidine and normorphine. It was much more than difficult to produce physical dependence on these drugs than it was to produce physical dependence on morphine.

Doctor Harris Isbell has developed an interest in the use of *N*-allylnormorphine as an analgesic. He obtained the drug, however, at a time when he was very much involved in conducting his studies on alcohol and barbiturate dependence. Lasagna and Beecher [10] did study the analgesic actions of nalorphine and found it to be nearly as potent as morphine. Dr. Abraham Wikler attempted to substitute nalorphine for morphine in a dependent subject and observed that it precipitated a violent abstinence syndrome that could not be antidoted by morphine. He subsequently characterized precipitated abstinence in humans and in the spinal dog [11, 12]. These observations provided an important clue in the development of nonaddicting, safer analgesics and were pursued by several pharmaceutical firms that synthesized a number of compounds with antagonistic effects.

Thus, the driving force for the enormous commitment for development of opioid antagonists as analgesics was that they had analgesic activity and did not appear to substitute for morphine in morphine-dependent subjects. It is important to recognize the importance of the substitution technique for identifying morphine-like drugs devised by Himmelsbach [13]. Although Himmelsbach did not couch his concepts in receptor theory, his work was one of the first critical pieces of evidence that strongly indicated that opioids were exerting their effects by acting through a common mechanism. Himmelsbach [14] attributes the development of this technique to the observations of Eddy [15], who demonstrated cross-tolerance between morphine, codeine, and heroin in the dog.

Himmelsbach reasoned that cross-dependence could also exist, and that dependence was a major determinant of the addictiveness of analgesics. He demonstrated that a number of morphine congeners substituted for morphine in morphine-dependant subjects. These studies had several major implications. One of the drugs studied by Dr. Himmelsbach was desomorphine. Desomorphine did not produce dependence in the monkey; it substituted for morphine in morphine-dependent subjects, however. This was to be only the first of several drugs with the ability to sustain dependence that was much greater in humans than in the monkey. These observations, and others, led to the suggestion that opioid receptors differed in the intimate details of their configuration from one species to another [16, 17].

Another important innovation was the application of bioassay statistical techniques to not only suppression and precipitation data but also to subjective effects data as assessed by questionnaires. Harris Isbell introduced this technique to help strengthen the conclusions that had been reached concerning the abuse potentiality of phenazocine, the first of a series of benzomorphans that had a critical role in the formulation of concepts concerning multiple opioid receptors. Phenazocine was much less potent than morphine as an analgesic in humans. In humans, however,

phenazocine was three to four times more potent than morphine in constricting pupils and producing subjective effects and was eight times more potent in suppressing abstinence [18].

In addition to emphasizing the large differences in response to opioids among species, several other important lessons were learned through this quantitative comparison between drug measure and species. (1) Different experimental variables (e.g., pupillary diameter vs. subjective effects) that were measured using different scales (e.g., ordinal, nominal, or ratio) yield potency estimates that were not only equivalent, but had similar confidence limits. (2) The use of dose–response relationships became an important criterion for identifying changes in subjective states that were relevant to the drug effects. (3) The concomitant use of both a physiologic and behavioral measure provided an internal validation of the behavioral measures [19]. The effects of opioids on subjective states became an important criterion for differentiating the receptor subtypes.

Isbell’s use of bioassay statistics and techniques to compare the relative potencies of opioids to suppress abstinence, to alter subjective states and to induce physiologic changes provided a powerful tool for quantitatively characterizing the pharmacologic profiles of drugs [18]. The use of crossover designs allowed for simultaneous and efficient assessment of relative potencies on several experimental parameters. Thus, valid assays could be obtained on studies employing four to six subjects using a four-point assay [20, 21]. This design allowed for the partitioning out of the between-subjects variance, and the error term for calculating the confidence limits of potency estimate was the residual part of the between-doses variance.

The seminal approach, however, had a major statistical problem in that different pharmacological effects were measured with different types of scales. For example, pupils were photographed and measured with a ruler (ratio scale). Some subjective states were measured using a nominal scale; others using an ordinal scale. Isbell’s first effort (Table 2.1) revealed that the confidence limits of the potency estimated for the different types of measurement scales were similar despite differences in the inherent properties of the scales.

From a practical and empirical perspective, potency estimates obtained from dose–response relationships employing data bearing on the frequency of occurrence of signs and symptoms using nominal scales, data bearing on the subjectively estimated intensity of feeling states using ordinal scales, and the measurement of pupillary diameter from Polaroid photographs were in close agreement and had similar confidence limits [19].

**Table 2.1** The relative potency of phenazocine and levophenacymorphan in comparison to morphine in constricting pupils (interval scale), altering signs and symptoms (nominal scale), and suppressing abstinence (mixed scale)<sup>a</sup>

	Pupils (miosis)	Questions	Suppression
Phenazocine	3.8 (1.3–5.6)	3.2 (2.3–5.0)	8.2 (4.2–17.2)
Levophenacymorphan (NIH-7525)	5.2 (2.7–8.0)	6.11 (5.0–7.5)	9.1 (4.8–20.0)

<sup>a</sup>From Fraser and Isbell [18]

These potency estimates further agreed with estimates of analgesic potency obtained in patients suffering from both acute and chronic pain. These observations were taken to mean that (1) the miotic phenomenon and changes in subjective states were probably the consequence of the drugs acting through a similar mechanism and that measures of subjective states were valid measures of drug effect; and (2) any lack of additivity among signs and symptoms, and deviations from linearity for nominal and ordinal scales, was probably small compared to between-subjects and across-time variance.

These latter issues were pursued experimentally. Thus, the frequency of occurrence of various signs or the intensity of symptoms and the degree of miosis produced by both morphine and heroin were found to be linearly related to the logarithm of dose. Hence, we knew that the principle of additivity was applicable to data obtained using nominal and ordinal ratio scales. We began to apply the criterion of dose responsiveness for the selection of questionnaire items [19, 22], yet another approach that enhances the rigor of additivity for our behavioral scales. Different signs were weighted such that the signs that exhibited lesser sensitivity were given greater weight. Thus, by weighting, different responses could be equated (e.g., pupils and liking).

The Himmelsbach method for scoring the intensity of opioid abstinence is composed of data derived from nominal, interval, and ratio scales that have different weighing values that are related to the severity of abstinence. A similar system for assessing abstinence was developed for precipitation and suppression studies in the dog [23, 24] that was composed of changes that were suppressed or precipitated in a dose-related way by agonists and antagonists and that were measured using nominal, ordinal, interval, and ratio scales. Those signs of abstinence, the frequency or intensity of which were related to the dose of the agonists in suppression studies and the dose of antagonists in the precipitation studies, were selected for measuring the intensity of abstinence, and each sign was weighted such that all signs made an approximately equal contribution to the abstinence syndrome score. Thus, the criterion of additivity and linearity were fulfilled.

By establishing linearity and additivity for items of subjective effects questionnaires, through a weighting and dosing relationship, a report of the two effects can be added. In a similar manner, the abstinence signs – yawning, piloerection, and body temperature – can be added. Through the technique of mapping, we have shown that there is a linear relationship between dose-related changes in score on the nominal, ordinal, interval, and ratio scales. This relationship is implicit when valid parallel line assays are obtained for different measures and effects. This is illustrated in Table 2.1.

These issues of measures and statistics have been discussed by Stevens [25]. Two important principles emerged. (1) Deviations from additivity and linearity for nominal and ordinal data are small compared to the unaccounted-for variance and (2) the frequency of occurrence of intensity of report are linearly related to the dose (logarithm) of the drug.

The use of pharmacologic syndromes has played a critical role in identifying receptor subtypes and in identifying specific drugs. In detailed studies of cyclazocine

in humans, it was apparent that cyclazocine produced effects that were not produced by morphine [26]. Although cyclazocine was a potent miotic (10–15 times or more potent than morphine and nalorphine), valid potency assays of this activity were not obtained. Further, cyclazocine in higher doses produced overt ataxia and subjects reported that they were sleepy and felt drunk. These signs and symptoms were not commonly observed in, or reported by, post addicts who had been administered morphine or heroin.

Cyclazocine and nalorphine produced feelings of well-being in some subjects, but not in others. They also produced feelings of dysphoric in more subjects when the dose was sufficient. The dysphoric effects of cyclazocine and nalorphine are complex. The most commonly reported symptom, with minimally dysphoric doses, is recall of disturbing memories. The patient can be distracted but has difficulty suppressing these thoughts. With larger doses, delusions, hallucinations, sleep with disturbing dreams, and anxiety states may be reported.

Cyclazocine was found to be 10–20 times more potent than morphine in equivalent measures. An attempt was made to make patients dependent on an equivalent dose of cyclazocine based on single-dose relative potency. A daily dose of 13.2 mg/70 kg was attained in six subjects. Some subjects found the dysphoric effects of cyclazocine especially disturbing and the dose of cyclazocine was incremented slowly. At the time these studies were initiated, we did not realize that cyclazocine had much longer duration of action than morphine, and hence our estimates of the equipotent dose of cyclazocine may have been high.

Regardless, when the administration of cyclazocine was terminated, we were presented with several surprises. The first was a long latency to onset of signs of abstinence. In fact, signs were not perceptible until the third day of withdrawal. Second, the abstinence syndrome was not associated with drug need. Most subjects were glad the study was over and none sought medication for relief of their symptoms. The third issue was the nature of abstinence syndrome.

Doctors Eddy and Isbell took the position that the cyclazocine abstinence syndrome was just mild abstinence. To help resolve this issue, Dr. Isbell provided me with unpublished data of E.G. Williams [27] who had studied the abstinence syndrome of subjects dependant on different stabilization doses of morphine in an attempt to determine the smallest dose of morphine that produced a clinically significant degree of physical dependence. A sign analysis of Williams' data and the cyclazocine abstinence data was done. The analysis indicated that the relative magnitude of the signs of cyclazocine abstinence was different from that of morphine abstinence, regardless of the level of dependence [26, 27].

The effects of cyclazocine shared certain characteristics with those of nalorphine [26], except that nalorphine was less potent and the maximum degree of ataxia was less. Whereas cyclazocine could produce overt drunkenness, nalorphine produced liminal ataxia that was only demonstrable with tandem gate walking. The latter difference was subsequently explained when studies were conducted in the chronic spinal dog, in which it was shown that nalorphine showed partial agonistic activity [24, 28]. When nalorphine was administered chronically in doses of 240 mg/kg/

day and then withdrawn, an abstinence syndrome emerged within 24 h and was qualitatively different from the morphine abstinence syndrome and similar to the cyclazocine abstinence syndrome.

Several investigators studied mixtures of morphine and nalorphine in human subjects and in animals, administered acutely and chronically [29]. Of particular importance were the observations of Houde and Wallenstein [30], who found that low doses of nalorphine antagonized the effects of 10 mg of morphine, whereas higher doses produced a lesser antagonism. The nalorphine biphasic dose response antagonism of morphine's analgesic action could not be explained by assuming that nalorphine was a competitive antagonist or a partial agonist of morphine. Houde and Wallenstein's observation [30] stimulated a mathematical formulation of receptor dualism [29, 31].

Naloxone antagonized the actions of cyclazocine in the chronic spinal dog [28] and in human subjects [32]. Naloxone in a high dose (15 mg/70 kg) antagonized miotic, respiratory depressant, and subjective effects produced by 1 mg/70 kg of cyclazocine in human subjects. Naloxone (0.2 mg/kg) partially antagonized the depressant effects of cyclazocine (0.063 mg/kg) on the flexor reflex of the chronic spinal dog. The same dose of naloxone completely antagonized the effects of 1.0 mg/kg of morphine. Blumberg showed that naloxone antagonized the analgesic effects of cyclazocine, nalorphine and pentazocine in mice [33].

Thus, four lines of evidence suggested that nalorphine and cyclazocine differed from morphine in their actions. (1) The nature of the subjective effects that they produced were different; (2) they produced different types of dependence; (3) interaction studies between morphine and nalorphine yielded biphasic dose response curves; and (4) the effects of several agonist-antagonists could be antagonized by large doses of naloxone.

These observations lead to the suggestions that there were two opioid receptors an M (morphine) and N (nalorphine). Further, the M and the N receptors operated in concert in some, but not all, physiologic systems. The process of a concerted action was "pharmacologic dualism." It was suggested that morphine acted as an agonist and nalorphine as a competitive antagonists at the M receptor. Further nalorphine acted as a partial agonist at the N receptor [29]. This concept (pharmacologic dualism) was an elaboration on my concept of pharmacologic redundancy, which postulated parallel neuronal pathways employing different transmitter, as well as co-transmitters and co-receptors as alternative mechanisms for the conduct of function [34].

The hypothesis that there are two opioid receptors that exhibit the principle of receptor dualism reconciled many observations. It was soon apparent, however, that it left other observations unexplained in terms of receptor theory.

The first analgesic with predominantly N agonistic activity to be marketed was pentazocine. It was not scheduled as a narcotic because studies at the Addiction Research Center indicated that it did not produce as much euphoria as morphine, did not substitute for morphine in morphine-dependent subjects, did not appear to produce physical dependence, and was not liked by post-addict subjects when administered chronically [35].

There were sporadic case reports of abuse of pentazocine. For this reason, and because we had developed new concepts, we decided to reinvestigate the abuse potentiality of pentazocine. One of the important developments in opioid pharmacology was the synthesis of naloxone and the elucidation of its pharmacology. Blumberg had encouraged the synthesis of naloxone with the end of obtaining a more potent antagonist with fewer side effects (e.g., respiratory depression and psychotomimetic effects) [36]. Foldes [37] conducted extensive studies with naloxone showing that it antagonized the respiratory actions of opiate analgesics. Lasagna found that naloxone produced a modest degree of both analgesia and hyperalgesia in patients with pain.

Our task was to assess the abuse potentiality of naloxone [38]. We found that it did not induce subjective changes, did not produce miosis when administered chronically, did not produce physical dependence, and, when administered to morphine-dependent subjects, was seven times more potent than nalorphine in precipitating abstinence [39]. We concluded that naloxone was an opioid antagonist that was devoid of agonistic activity. Naloxone was of great importance in further clarifying the mechanism of action of pentazocine and provided critical proof that morphine was acting as an agonist.

In our reinvestigations of pentazocine, we confirmed several of the observations of Fraser and Rosenberg [35]. Low doses of pentazocine produced a subjective state similar to that produced by low doses of morphine characterized by elevations of MBG scale scores, which measure feelings of well-being. In this regard, pentazocine was about one-fourth as potent as morphine [40]. Further, doses above 40 mg produced dose-related elevation on the LSD and PCAG scale scores, which measure, respectively hallucinations, delusions, and anxiety (LSD) and apathetic sedation (PCAG), and a decrease in the MBG scale scores.

The fact that lower doses of pentazocine produced elevations of MBG scale scores raised the question of whether pentazocine could be a weak partial agonist at the M receptor and a less potent but strong agonist, at the N receptor. To test this hypothesis, subjects were made dependant on decreasingly lower doses of morphine and the ability of pentazocine to suppress the morphine and abstinence syndrome was assessed. In short, pentazocine did not clearly suppress abstinence in subjects dependent on morphine in doses as low as 30 mg/day and as high as 240 mg/day.

When subjects who were dependent and stabilized on 240 mg/day of morphine were administered pentazocine, it precipitated an abstinence syndrome and in this regard was 1/50 as potent as nalorphine. Thus the doses of pentazocine that were necessary to precipitate abstinence were greater than those necessary to cause miosis, analgesia, and subjective effects. When subjects were administered pentazocine in doses of 522–684 mg/day and then abruptly withdrawn, a mild abstinence syndrome emerged that was quantitatively similar to that seen in cyclazocine- and nalorphine-dependent subjects.

Further, an abstinence syndrome could be precipitated in pentazocine-dependent subjects with naloxone in doses approximately ten times larger than necessary to precipitate an abstinence syndrome in morphine-dependent subjects. At this

juncture our operating hypothesis was that pentazocine, like nalorphine and cyclazocine, was a competitive antagonist at the M receptor and either a partial or a strong agonist at the N receptor.

We had been aware that cyclazocine and nalorphine produced a subjective syndrome consisting of dysphoria and an apathetic sedation. The fact that pentazocine produced more feeling of well-being than did nalorphine and cyclazocine, and yet resembled them in many other ways, was a problem – “the pentazocine problem.”

To determine if this problem had a receptor-based explanation, an extensive group of studies was initiated in the chronic spinal dog [23, 41–43]. These studies developed methods that yielded data in the dog that provided potency estimates on a variety of physiologic parameters (pupillary diameter, pulse rate, respiratory rate, body temperature, amplitude of the flexor reflex, and the latent of the skin twitch reflex). In addition, procedures were developed for conducting valid assays of the potency of drugs in suppressing signs of abstinence in the maximally abstinent chronic spinal dog.

A large group of dogs was made dependent on morphine; a prototypic “M” agonist. Another group was made dependant on cyclazocine; a prototypic “N” agonist. Over 20 prototypic drugs were studied. Morphine-like drugs (see Table 2.2) by and large produced a similar pattern of effects suppressing the flexor and skin twitch reflexes, constricting pupils, lowering body temperature, and slowing pulse rate. Further these agents as well as other that resembled morphine suppressed the morphine abstinence syndrome in a dose-related way. Of some importance were the observations that neither meperidine nor normorphine produced morphine-like effects or suppressed the morphine abstinence syndrome. Hence, although they are morphine-like drugs in other species, they do not appear to be morphine-like in the dog.

Buprenorphine in single doses also produced a morphine-like pattern of effects, but differed from morphine in that it produced a lesser maximal effect. Further it suppressed abstinence signs; the slope of its suppression dose–response line was less than that of morphine, however. Buprenorphine also precipitated abstinence in stabilized morphine-*dependent* dogs; the slope of the precipitation dose-response line, however, was less than that of naloxone and naltrexone. These data were consistent with the hypothesis that the buprenorphine was a partial agonist of the morphine-type.

In contrast to morphine-like drugs, cyclazocine, nalorphine, and pentazocine were relatively ineffective in suppressing the thermally evoked skin twitch reflex, but produced a profound depression of the pressure-evoked flexor reflex. They also, especially in longer doses, dilated pupils and increased heart and respiratory rate, but did not depress body temperature to the degree morphine did.

Keats and Telford [44] in their study of the analgesic properties of a series of *N*-substituted benzomorphans, had observed that *N*-allylnormetazocine (NANM; SKF 10,047) produced severe dysphoria and little analgesia. NANM was selected as a prototypic and relatively selective dysphoriant and was studied in the chronic dog. It produced less depression of the flexor reflex than morphine or ethylketazocine, did not depress the skin twitch reflex, increased pupillary diameter, pulse rate, and respiratory rate, and produced a canine delirium.

**Table 2.2** Relative potency of  $\mu$  and  $\kappa$  agonists in suppressing and precipitating abstinence in morphine (A)- and cyclazocine (B)- dependent dogs and in producing changes in the nondependent dog (C)<sup>a</sup>

Drug	Morphine-dependent dogs		Cyclazocine-dependent dogs		
	(A)		(B)	(C)	
	Suppression potency	Precipitation potency	Suppression potency	Precipitation potency	Single dose
D-Propoxyphene	0.2				0.12
Propiram					0.14
Codeine					0.06–0.1
Morphine	1.0		1		1
Oxycodone	1.2				
Methadone	4.9				
Ketobemidone	5.1				
Phenazocine	8.1				
Levorphanol	9.0				
Dilaudid	15.4				
Fentanyl	70.5				
Etorphine	200.3				
Buprenorphine					257
Pentazocine		0.002	0.19		0.3
Nalorphine		0.08	0.24 (PA)	0.009	0.5
<i>N</i> -allylnormetazocine (NANM)		0.13			
Cyclazocine		0.47	1.0		3.3
Naloxone		1			
Naltrexone		3.4		1	0
Ethylketazocine			4.41		9
Ketazocine			0.2		1

PA nalorphine is a partial agonists

<sup>a</sup>Potency estimates for suppression studies are expressed as milligrams of morphine or cyclazocine that are necessary to produce the same degree of suppression as the experimental drug. Naloxone is used as a standard drug in precipitation studies in morphine-dependent dogs and naltrexone in cyclazocine-dependent dogs

NANM's respiratory stimulant action probably has a different mechanism of action than morphine's in the dog. Morphine causes panting by resetting hypothalamic thermoregulatory center that downregulated the set point and thus body temperature. In contrast, NANM stimulated respiration, while producing a modest hyperthermic reaction. In all probability the respiratory stimulant actions of nalorphine, which are seen in relatively high doses, are a consequence of nalorphine's  $\sigma$  activity [41].

Other prototypic drugs studied were ketazocine and ethylketazocine, which depressed the flexor reflex, had little effect on the latency of the skin twitch reflex, produced sedation, and were potent miotics.

Studies in the morphine- and cyclazocine-dependent dog are summarized in Table 2.2. Several points are of importance. Nalorphine precipitated abstinence in both

the morphine- and cyclazocine-dependent dog. In the cyclazocine-dependent spinal dog, however, it exhibited a ceiling effect. These observations were in keeping with the observations in the nondependent dog, namely that nalorphine's agonistic effects exhibited a ceiling and that it was probably a partial agonist of the  $\kappa$  type (see below).

Of great importance were the observations that three groups of drugs suppressed the cyclazocine abstinence: (1) morphine; (2) cyclazocine, nalorphine, and pentazocine, which exhibited excitation effects such as mydriasis and tachycardia; and (3) ethylketazocine and ketazocine, which constricted pupils, but did not suppress the morphine abstinence syndrome. The excitatory effects of cyclazocine, nalorphine, and (to some extent) pentazocine resemble the effects of NANM.

To further compare the pharmacologic properties of NANM with those of the prototypic drugs, morphine and cyclazocine dogs were made dependent on 10 mg/kg/day of NANM administered in equally divided i.v. doses six times a day [43]. This proved to be a difficult experiment to execute. As the dose levels were increased, dogs exhibited canine delirium and loss of appetite and weight. By slowly escalation the dose, a stabilization dose of 10 mg/kg was eventually obtained, and precipitation and withdrawal studies were conducted.

This study showed that chronic administration of NANM induced tolerance to its ability to produce canine delirium, tachypnea, and anorexia. The withdrawal abstinence was mild, consisting of a decrease in body temperature, miosis, brachycardia, tachypnea, and an increase in the amplitude of the flexor reflex. This syndrome was unlike that seen in either morphine- or cyclazocine-dependent animals. The naltrexone-precipitated abstinence syndrome was yet different, consisting of hyperthermia, tachycardia, tachypnea, and an increase in the amplitude of the flexor reflex. These data further showed that some of the effects of chronically administered NANM could be antagonized by naltrexone, whereas others could not. These observations led to the suggestion that NANM might have multiple modes of action.

These and other observations could be reconciled by the hypothesis that (1) there were three opioid-related receptors,  $\mu$ ,  $\kappa$ , and  $\sigma$  [41]; (2) these receptors could exert their effects on several physiologic systems through different but converging pathways (receptors dualism and pharmacologic redundancy) [29]; and (3) drugs that interact with opioid receptors could act as competitive antagonists partial agonists and strong agonist.

## 2.2 Reflections

In the relatively brief time – two decades – since these hypotheses were proposed, an enormous body of data has been generated that supports them. Further, they have been extended in two major directions: (1) additional types of opioid-related receptors have been identified and (2) endogenous opioid transmitter substances have been discovered. These observations have had, and will continue to have, an enormous impact on neurochemistry, physiology, neuropsychopharmacology, and psychology, as well as on mental health.

### 2.2.1 Pharmacologic Implications

The first clues concerning the existence of multiple opioids came from studies in humans that were subsequently elaborated on using the chronic spinal dog. The conclusions were drawn from analyses of the patterns of pharmacologic effects using agonists and antagonists of different specificities and differed from other classic analyses of receptor subtypes only in that these comparisons used signs derived from changes in central nervous function for the comparisons. For these pattern comparisons to become meaningful, valid bioassay techniques had to be developed for the various central nervous system functions under study such as subjective effects, pupillary diameter, function of homeostats, and reflex activity. The second element was the use of receptor theory in the design of experiments and conceptualization of hypotheses. The third major ingredient in this endeavor was the very large synthetic effort that yielded a rich diversity of structural modification of important drugs. In this regard the synthetic efforts of Sidney Archer, William Michne, Jack Fishman, John Lewis, and Everett May were particularly important.

In a relatively short time, it was demonstrated that relatively minor structural modifications of opioid drugs could change the specificities for  $\mu$ ,  $\kappa$ ,  $\sigma$ , and  $\delta$  receptors and could alter their activity, yielding agonists, partial agonists, and competitive antagonists. It was also apparent that opioid ligands had a number of reactive sites that could interact with a variety of moieties on opioid receptors. These general observations lead to the formulation of the steric theory of multiple opioid receptors, which offers a theoretical basis for explaining not only the multiplicity of opioid receptors but also differences in their efficacy and activity [17].

The steric theory has several components:

1. It assumes that the opioid receptor has nuclear sites that are responsible for initiating the pharmacologic action of the drug or transmitter, as well as satellite sites that play two roles: (a) determination of the affinity of the drug for the receptor and (b) the orientation of the drug on the receptors.
2. Changes in the configuration of these two components of the receptors may have several effects on drug receptor interactions. The following terms are coined to designate the possible types of changes. *Allomorphism* is a change in the position of the active moieties of the nuclear part of the receptor. Such changes will result in a change in the specificity of drugs for the receptor. *Allosterism* is a change in the positions of moieties of the satellite sites. These result in changes of affinity of the drug for the receptor and in the orienting properties of the receptor toward the drug. *Allotaxia* is the property whereby the drug can occupy the receptor in several positions.

These types of changes in the receptors can hypothetically be interactive. Clearly, changes in the relative positions of satellite moieties could alter both the affinity and the allotaxic properties of a family of drugs and hence alter both the  $K_d$  values and the activity of the drug. On the other hand, allomorphic changes will result in a change in the number of receptors of different specificities. These types of changes may result in complicated dose–response curves.

Depending on one's perspective, the concept of opioid antagonists had a slow acceptance by the medical and pharmacologic community. The concept of multiple opioid receptors and the application of receptor theory to opioids had a somewhat more rapid acceptance. The delineation of each receptor subtype has extended our basic understanding of general receptor theory, as well as the complexity of body function and evolution. In turn, the complexities of microstructure and function have provided those who have a bent for using pharmacologic approaches to function and evolution a wonderful opportunity for identifying drugs with unique specificities. I believe that a strong case can be made for the proposition that the discovery of most multiple receptors types has been a consequence of pattern identification using tissues of diverse origins and response drugs.

I have tried in this account to present most of the critical events that either directly or indirectly have influenced my thinking and conclusions about multiple opioid receptors and receptor dualism. It was my very good fortune to have had Drs. Klaus Unna, Harris Isbell, and Abraham Wikler as my teachers, collaborators, and friends. They played critical roles and had seminal influences in the development of opioid antagonists and agonist-antagonists as therapeutic agents and pharmacologic tools. They also recognized the importance of systematic, quantitative, and reliable observations in drug comparison, both in humans and animals, a perspective that was essential to the analysis of the mechanisms of action of opioid receptors.

## References

1. Eddy NB, May EL (1973) The search for a better analgesic. *Science* 181:407-414
2. Von Braun J (1916) Unter suchungdn uber morphium-alkalvide. III. Mitteilung. *Berlin Deut Chem Ges* 49:977-989
3. Pohl J (1915) Ueber das *N*-allylnorcodeine, einin antagonisten des morphins. *Z Exp Pathol Ther* 79:370-382
4. Meissner R (1923) Uber Atmungserrgende heilmittel. *Z Gesamte Exp Med* 13:245-258
5. Leake CD (1967) Introduction. In: Way EL (ed) *New concepts in pain and its clinical management*. F.A. Davis Co., Philadelphia
6. Weijlard J, Erickson AE (1942) *N*-allylnormorphine. *J Am Chem Soc* 64:869-870
7. Hart ER, McCauley EL (1944) The pharmacology of *N*-allylnormorphine as compared with morphine. *J Pharmacol Exp Ther* 82:339-348
8. Unna K (1943) Antagonistic effect of *N*-allylnormorphine upon morphine. *J Pharmacol Exp Ther* 79:27-31
9. Eckenhoff JE, Elder JD, King BD (1952) *N*-allylnormorphine in treatment of morphine or demerol narcosis. *Am J Med Sci* 223:191-197
10. Lasagna L, Beecher HK (1954) Analgesic effectiveness of nalorphine and nalorphine-morphine combinations in man. *J Pharmacol Exp Ther* 112:356-363
11. Wikler A, Fraser HF, Isbell H (1953) *N*-allylnormorphine: effects of single doses and precipitation of acute abstinence syndromes during addiction to morphine; methadone or heroin in man (post addicts). *J Pharmacol Exp Ther* 109:8-20
12. Wikler A, Carter RL (1953) Effects of single doses of *N*-allylnormorphine on hindlimb reflexes of chronic spinal dogs during cycles of morphine addiction. *J Pharmacol Exp Ther* 109:92-101
13. Himmelsbach CK (1939) Studies of certain addiction characteristics of: (a) dihydromorphine ("paramorphan"), (b) dihydrodesoxymorphine-D ("desomorphine"), (c) dihydrodesoxicodeine-D

- ("desocodeine"), (d) methyldihydromorphinone ("metopon"). *J Pharmacol Exp Ther* 67:239–249
14. Himmelsbach CK (1978) Summary of chemical, pharmacological, and clinical research. In: Martin WR, Isbell H (eds) *Drug addiction and the U.S. Public Health Service*. National Institute on Drug Abuse, Washington, DC
  15. Downs AW, Eddy NB (1928) Morphine tolerance. II. The susceptibility of morphine-tolerant dogs to codeine, heroin, and scopolamine. *J Lab Clin Med* 13:745
  16. Martin WR, Jasinski DR (1977) Assessment of the abuse potential of narcotic analgesics in animals. In: Martin WR (ed) *Drug addiction I*. Springer, Berlin
  17. Martin WR (1983) Pharmacology of opioids. *Pharm Rev* 35:283–323
  18. Fraser HF, Isbell H (1960) Human pharmacology and addiction liabilities of phenazocine and levophenacymorphan. *Bull Narc* 12:15–23
  19. Martin WR, Fraser HF (1961) A comparative study of physiological and subjective effects of heroin and morphine administered intravenously in postaddicts. *J Pharmacol Exp Ther* 133:388–399
  20. Bliss CI (1952) *The statistics of bioassays: with special reference to the vitamins*. Academic, New York
  21. Finney DJ (1964) *Statistical methods of biological assay*, 2nd edn. Hafner, New York
  22. Martin WR, Sloan JW, Sapira JD et al (1971) Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clin Pharm Ther* 12:245–258
  23. Martin WR, Eades CG, Thompson WO et al (1974) Morphine physical dependence in the dog. *J Pharmacol Exp Ther* 189:759–771
  24. Martin WR, Eades CG, Thompson JA et al (1976) The effects of morphine and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J Pharmacol Exp Ther* 197:517–532
  25. Stevens SS (1968) Measurement, statistics, and the schemapiric view: like the faces of Janus, science looks two ways – toward schematics and empirics. *Science* 161:849–856
  26. Martin WR, Gorodetzky CW (1965) Demonstration of tolerance to and physical dependence on *N*-allylnormorphine (nalorphine). *J Pharmacol Exp Ther* 150:437–442
  27. Martin WR (1966) Assessment of the dependence producing potentiality of narcotic analgesics. In: Radouco TC, Lasagna L (eds) *International encyclopedia of pharmacology and therapeutics*. Pergamon, Glasgow
  28. McClane TK, Martin WR (1967) Antagonism of the spinal cord effects of morphine and cyclazocine by naloxone and thebaine. *Int J Neuropharmacol* 6:325–327
  29. Martin WR (1967) Opioid antagonists. *Pharm Rev* 19:463–521
  30. Houde RW, Wallenstein SL (1956) Clinical studies of morphine-nalorphine combinations. *Fed Proc* 15:440–441
  31. Martin WR, Gorodetzky CW, Thompson JA (1972) Receptor dualism: some kinetic implications. In: Kosterlitz HW, Collier HOJ, Villarreal JE (eds) *Agonist and antagonists actions of narcotic analgesic drugs: Proceedings of the symposium of the British Pharmacological Society, Aberdeen, July 1971*
  32. Jasinski DR, Martin WR, Sapira JD (1968) Antagonism of the subjective, behavioral, pupillary, and respiratory depressant effects of cyclazocine by naloxone. *Clin Pharm Ther* 9:215–222
  33. Blumberg H, Wolf PS, Dayton HB (1965) Use of writhing test for evaluating analgesic activity of narcotic antagonists. *Proc Soc Exp Biol Med* 118:763–766
  34. Martin WR (1970) Pharmacological redundancy as an adaptive mechanism in the central nervous system. *Fed Proc* 29:13–18
  35. Fraser HF, Rosenberg DE (1964) Studies on the human addiction liability of 2-hydroxy-5, 9-dimethyl-2-(3,3 dimethylallyl)-6-7-benzomorphan (Win 20 228): a weak narcotic antagonist. *J Pharmacol Exp Ther* 143:149–156
  36. Blumberg H, Dayton HB (1973) Naloxone, naltrexone, and related noroxymorphones. *Adv Biochem Psychopharmacol* 8:33–43

37. Foldes FF, Lunn JN, Moore J et al (1963) *N*-allylnoroxymorphone: a new potent narcotic antagonist. *Am J Med Sci* 245:23–30
38. Lasagna L (1965) Drug interaction in the field of analgesic drugs. *Proc R Soc Med* 58:978–983
39. Jasinski DR, Martin WR, Haertzen CA (1967) The human pharmacology and abuse potential of *N*-allylnoroxymorphone (naloxone). *J Pharmacol Exp Ther* 157:420–426
40. Jasinski DR, Martin WR, Hoeldtke RD (1970) Effects of short- and long-term administration of pentazocine in man. *J Pharmacol Exp Ther* 11:385–403
41. Gilbert PE, Martin WR (1976) The effects of morphine and nalorphine-like drugs in the non-dependent, morphine-dependent and cyclazocine-dependent chronic spinal dog. *J Pharmacol Exp Ther* 198:66–82
42. Martin WR, Gilbert PE, Thompson JA, Jessee CA (1978) Use of the chronic spinal dog for the assessment of the abuse potentiality and utility of narcotic analgesics and narcotic antagonists. *Drug Alcohol Depend* 3:23–25
43. Martin WR, Eades CG, Gilbert PE et al (1980) Tolerance to and physical dependence on *N*-allylnormetazocine (NANM) in chronic spinal dogs. *Subst Alcohol Actions Misuse* 1:269–279
44. Keats AS, Telford J (1964) Narcotic antagonists as analgesics. In: Gould RF (ed) *Molecular modification in drug design*. Advances in chemistry series No. 45. Washington, DC: American Chemical Society



<http://www.springer.com/978-1-60761-992-5>

The Opiate Receptors

Pasternak, G. (Ed.)

2011, XII, 516 p., Hardcover

ISBN: 978-1-60761-992-5

A product of Humana Press