*Br. J. clin. Pharmac.* (1979), 7, 273S–279S

# HISTORY AND DEVELOPMENT OF MIXED OPIOID AGONISTS, PARTIAL AGONISTS AND ANTAGONISTS

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1 A brief history of the development of narcotic antagonists is outlined.

2 The clinical and pharmacological observations leading to the discovery of dualism of opiate receptors are reviewed.

3 An extension of this theory to a three-receptor model ($\mu$, $\kappa$ and $\sigma$) is required to rationalize the pharmacology of the antagonist analgesics cyclazocine, pentazocine and nalorphine.

4 The methodologies available for the study of compounds with dual agonist–antagonist activity are discussed in the light of the above receptor multiplicity, and data appertaining to the $\kappa$-partial agonist, nalorphine and the $\mu$-partial agonist buprenorphine are outlined.

## Introduction

I WOULD first like to express my gratitude for the honour that has been extended in inviting me to address this meeting of anaesthesiologists and to briefly relate the history of current concepts concerning opioid agonists–antagonists. The story begins with Pohl (1915) who, on the assumption that allyl compounds stimulated respiratory processes, studied N-allylnorcodeine and demonstrated that it not only antagonized the effects of morphine and heroin, but also had direct respiratory stimulant actions in its own right. The observations of Pohl went unattended until Hart (1941) and Hart & McCawley (1944) synthesized N-allylnormorphine (nalorphine) and studied its effects. This work was partially supported by Merck who concurrently initiated efforts to synthesize nalorphine (Weijlard & Erickson, 1942), and their preparation was studied by Unnal (1943). Nalorphine was also found to antagonize the effects of morphine. Eckenhoff *et al.* (1951) demonstrated that nalorphine was an antidote for morphine poisoning in man. Shortly thereafter, Wikler *et al.* (1953) demonstrated that nalorphine could precipitate abstinence in morphine-dependent subjects. Isbell & Fraser (1950) suggested that nalorphine might be a clinically useful analgesic and Lasagna & Beecher (1954) found that nalorphine was a potent analgesic. These latter observations stimulated the study of narcotic antagonists as potentially non-addicting analgesics. Many compounds were synthesized, some of which were studied in man. Nalorphine received only a limited clinical trial primarily because doses which produced analgesia also produced dysphoric effects. Archer *et al.* (1962) and Harris & Pierson (1964) synthesized and studied the effects of several benzomorphan derivatives. The first narcotics with this structure were synthesized in the laboratory of Dr Nathan B. Eddy by Dr Everett May (May & Ager, 1959). At the time Archer and Harris began their work it was known that several substitutions, in addition to the allyl group, on the nitrogen of morphine and related chemicals, gave rise to drugs that had antagonistic properties.

Two compounds that Archer and Harris studied became of clinical importance: pentazocine and cyclazocine. Fraser & Rosenberg (1964) carried out a definitive study of the abuse potentiality of pentazocine and preliminary studies of the abuse potentiality of cyclazocine. Martin *et al.* (1965) and Martin & Gorodetzky (1965) continued these studies of cyclazocine and re-investigated the abuse potentiality of nalorphine. During the course of these studies, several observations were made. It was noted that cyclazocine and nalorphine differed from morphine in that they produced different constellations of signs and symptoms. Such signs and symptoms as itchy skin, coasting and soapboxing (talkativeness) were prominent parts of the morphine syndrome, whereas sleepiness and drunkenness were prominent parts of the cyclazocine syndrome. Further, patients receiving large doses of cyclazocine and nalorphine reported feelings of dysphoria.

0306–5251/79/150273–07 $01.00

Whereas cyclazocine produced gross ataxia, nalorphine produced only a modest impairment of heel to toe walking. It was only later when we discovered that nalorphine was a $\kappa$ partial agonist, whereas cyclazocine was a strong agonist at the $\kappa$-receptor, that this difference was explained. Chronic administration of both cyclazocine and nalorphine induced tolerance to their ability to produce sedation, ataxia and dysphoria. When withdrawn, an abstinence syndrome emerged that differed from that observed after withdrawal of morphine in morphine-dependent subjects. The most prominent part of the cyclazocine abstinence syndrome was an increase in body temperature and there was little hyperpnoea and hypertension compared with the morphine abstinence syndrome.

On a theoretical basis, we were perplexed by the observations of Houde & Wallenstein (1956), who studied various combinations of morphine and nalorphine. They found that lower doses of nalorphine antagonized the analgesic effects of morphine, whereas larger doses of nalorphine produced a lesser degree of antagonism.

This observation was not consistent with the hypothesis that nalorphine was a partial agonist of the morphine type. At this time we came to the conclusion that there must be two distinguishable receptors responsible for the analgesic effects of morphine on the one hand, and nalorphine and cyclazocine on the other; and that nalorphine and cyclazocine were competitive antagonists of morphine at the morphine receptor and agonists at the nalorphine receptor. We called this situation receptor dualism and suggested that a drug could be a strong agonist, a partial agonist or a competitive antagonist at either of these receptors. On a theoretical basis, it was also found that the two-receptor theory explained the biphasic interaction curve between morphine and nalorphine obtained by Houde & Wallenstein (1956), Martin (1967) and Martin *et al.* (1972).

Yet another important drug in the development of concepts related to the mode of action of agonist – antagonists was naloxone. Our clinical studies of naloxone (Jasinski *et al.*, 1967) revealed that it was devoid of morphine- as well as nalorphine- and cyclazocine-like agonistic activity. It was also less potent in antagonizing the agonistic actions of cyclazocine in the chronic spinal dog (McClane & Martin, 1967a) and in man (Jasinski *et al.*, 1968) than the agonistic actions of morphine and in precipitating abstinence in the cyclazocine dependent dog (Gilbert & Martin, 1976a), and pentazocine-dependent men (Jasinski *et al.*, 1970) than in morphine-dependent men or dogs.

These observations also were consistent with the hypothesis that the nalorphine-type receptor was different from the morphine receptor. Naloxone was a critical drug for its absence of agonistic activity clearly argued against the view that narcotic antagonists exerted their antagonist effect through a stimulant action, a view held by some.

Keats & Telford (1966) showed that although nalorphine depressed respiration in man, it exhibited a ceiling effect. McClane & Martin (1967b) also found that nalorphine partially depressed the flexor reflex of the chronic spinal dog with maximum depression occurring with a dose of 1 mg/kg. Although 1, 4 and 16 mg/kg produced the same amount of depression of the flexor reflex, 64 mg/kg produced a lesser degree of depression (Figure 1) (Gilbert & Martin 1976b). These data indicated that nalorphine was a partial agonist, a point to which we shall return.

Several disturbing observations gave us reason to believe that the two-receptor theory did not fully explain the action of cyclazocine, pentazocine and nalorphine. First, there were subtle differences in the cyclazocine, nalorphine and pentazocine abstinence syndromes; second, pentazocine was unable to suppress morphine abstinence despite the fact that the subjective effects that it produced seemed to be morphine-like. In an attempt to demonstrate that pentazocine had morphine-like activity, Jasinski (unpublished observations) made subjects dependent on morphine 30 and 60 mg daily and was unable to suppress abstinence with any dose of pentazocine that he studied. The proposal that pentazocine was a partial agonist of the morphine type and a stronger agonist of the nalorphine type (Jasinski *et al.*, 1970; Martin & Jasinski, 1972) was thus untenable. Subsequent studies in the chronic spinal dog revealed that there were three opioid receptors: a $\mu$ receptor which is responsible for a supraspinal type of analgesia, feelings of well being and at least an important part of morphine-type physical dependence; a $\kappa$ receptor which is responsible for spinal analgesia, sedation and anaesthesia and many of the signs of cyclazocine dependence; and a $\sigma$ receptor which is responsible for feelings of dysphoria, mydriasis and respiratory stimulation. Pentazocine proved to be a weak competitive antagonist of the $\mu$ type, a strong $\kappa$ agonist and a $\sigma$ agonist (Martin *et al.*, 1976; Gilbert & Martin, 1976a).

The term agonist–antagonist as applied to opioid analgesics and their central nervous system actions has thus come to involve two concepts: (1) the concepts of multiple receptors and receptor dualism; (2) the concept of the partial agonists. The concept of multiple receptors has been firmly established in the peripheral nervous system for cholinergic and adrenergic drugs. It seems that there are also multiple enkephalinergic and endorphinergic receptors. The concept of receptor dualism (Martin, 1967), however, is a new one which concerns itself with the interaction of multiple agonists and antagonists

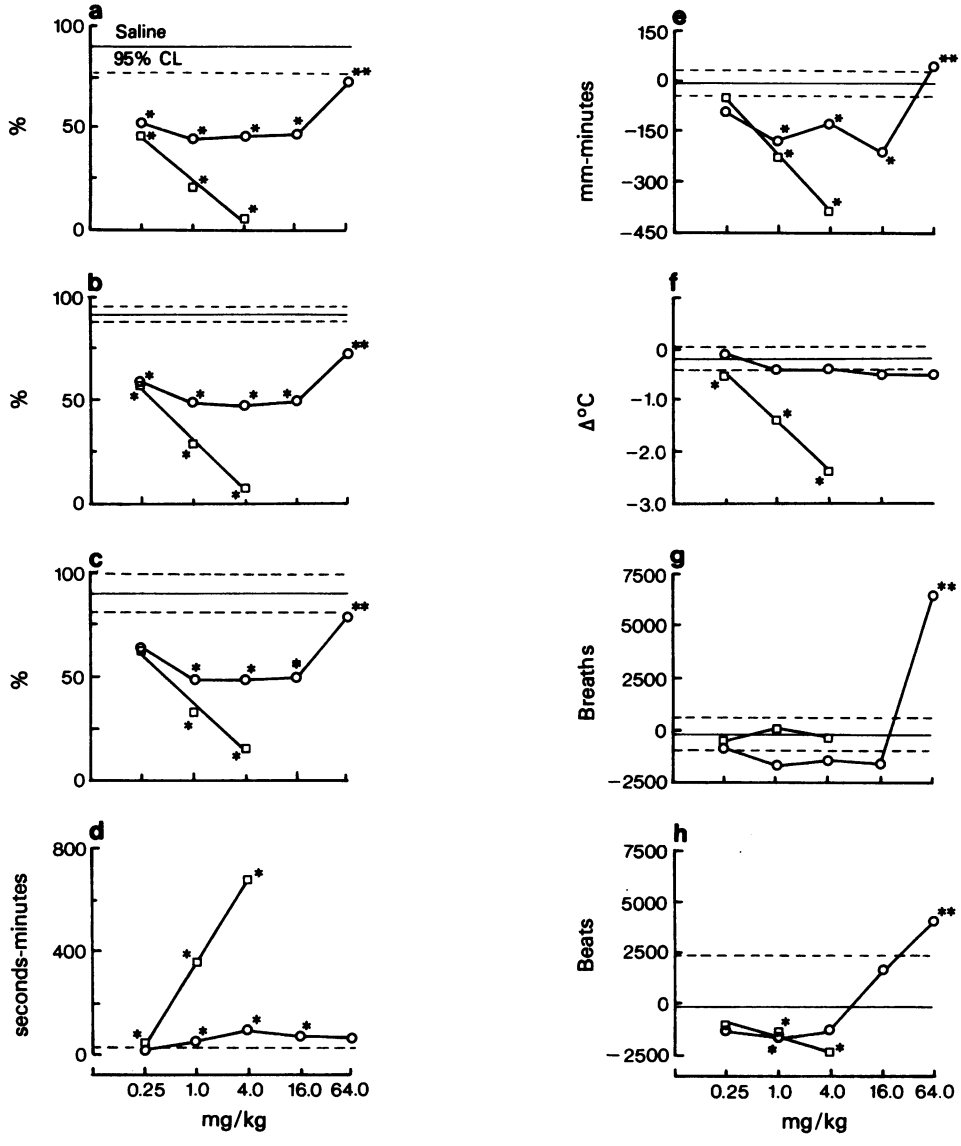


**Figure 1** Effects of morphine (□) and nalorphine (○) in six non-dependent chronic spinal dogs. *Significantly different from saline ($P < 0.05$); **significantly different from nalorphine 16 mg/kg. (From Gilbert & Martin, 1976b.) *a*, Flexor reflex, low stimulus (4,5 psi); *b*, medium stimulus (9 psi); *c*, high stimulus (18 psi); *d*, skin twitch; *e*, pupils; *f*, body temperature; *g*, respiration; *h*, pulse.

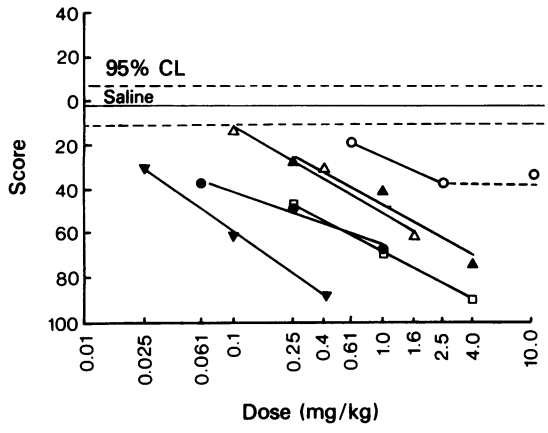


**Figure 2** Suppression of abstinence in cyclazocine-dependent dogs. Each point represents the mean of determinations made in six animals. ▼, WIN 35, 197-2; ●, cyclazocine; □, morphine; △, ketocyclazocine; ▲, pentazocine; ○, nalorphine. (From Gilbert & Martin, 1976a.)

which alter the function of a single experimental parameter such as pain through different neuropharmacological mechanisms.

Drugs such as cyclazocine and pentazocine seem to be mixed, strong agonists and competitive antagonists. Naloxone is a competitive antagonist which has different affinities for different receptors.

I would now like to return to the issue of partial agonists and discuss partial agonists of the opioid type and the methodologies for studying them. The classic way of demonstrating that a drug is a partial agonist is to show that its dose–response curve has a lesser slope than a strong agonist, that it exhibits a ceiling effect and that it can partially antagonize the effects of large doses of a strong agonist. On the basis of theoretical considerations about the nature of opioid tolerance and dependence, it was concluded that opioids continue to exert their full agonistic action in the tolerant and dependent animal and that this agonistic action was manifested by the suppression of the abstinence syndrome (Martin, 1967, 1968, 1970; Martin & Sloan, 1977). Three correlaries of this proposition were (1) that partial agonists could suppress abstinence in subjects with low levels but not high levels of dependence; (2) that partial agonists would precipitate abstinence in subjects with a high level but not a low level of dependence; and (3) that, in a maximally dependent subject, a partial agonist precipitation dose–response curve would have a lesser slope than that of a competitive antagonist and in an abstinent subject the suppression dose–response curve of a partial agonist would have a lower slope than that of a strong agonist.

We have already discussed some of the single dose data obtained with nalorphine that have indicated that it was a partial agonist of the $\kappa$ type. Nalorphine did not suppress abstinence in the morphine-dependent chronic spinal dog, but rather precipitated it. However, in the cyclazocine-dependent chronic spinal dog, it partially suppressed abstinence in that a ceiling effect was observed (Figure 2). This experiment supports the view that nalorphine is a competitive antagonist at the $\mu$ receptor and a partial agonist at the $\kappa$ receptor.

Buprenorphine, in contrast to nalorphine, appears to be a partial agonist of the $\mu$ (morphine) type in the chronic spinal dog. As can be seen in Figure 3, a ceiling effect was obtained for suppression of the flexor reflex and constriction of pupils. It is approximately 100 times more potent than morphine. Further, buprenorphine suppressed withdrawal signs in the abstinent morphine-dependent chronic spinal dog; but the slope of the dose response was less than that of morphine or d-propoxyphene (Figure 4). Buprenorphine also precipitated abstinence in the stabilized morphine-dependent chronic spinal dog, but the dose–response line had a lesser slope than did the naloxone dose–response relationships (Figure 5). Chronic spinal dogs were also administered buprenorphine chronically at a dose of 0.1 mg/kg daily. As buprenorphine was found to be approximately 100 times more potent than morphine, this dose level was comparable to that of morphine commonly administered chronically. The buprenorphine withdrawal syndrome was quite mild. Naloxone precipitated a mild abstinence syndrome in the buprenorphine-dependent chronic spinal dog but was less than 1/30 as potent in precipitating withdrawal signs as it was in precipitating abstinence in morphine-dependent dogs. These observations are also consistent with the view that buprenorphine is a partial agonist of the $\mu$ (morphine) type.

It now seems that the term agonist–antagonist as it applies to the opioid analgesics has two meanings. The term can indicate that the drug is a partial agonist of a certain type (for example $\mu$, $\kappa$ or $\sigma$). This is the generally accepted meaning of the term. Another meaning of the term has emerged and is related to the concept of multiple receptors and receptor dualism. In this context, the drug can be an agonist (either partial or strong) at one receptor and an antagonist (either a partial agonist or a competitive antagonist) at another receptor.

## Conclusions

It now seems that opioid analgesics act as agonists interacting with several closely related receptors. It is

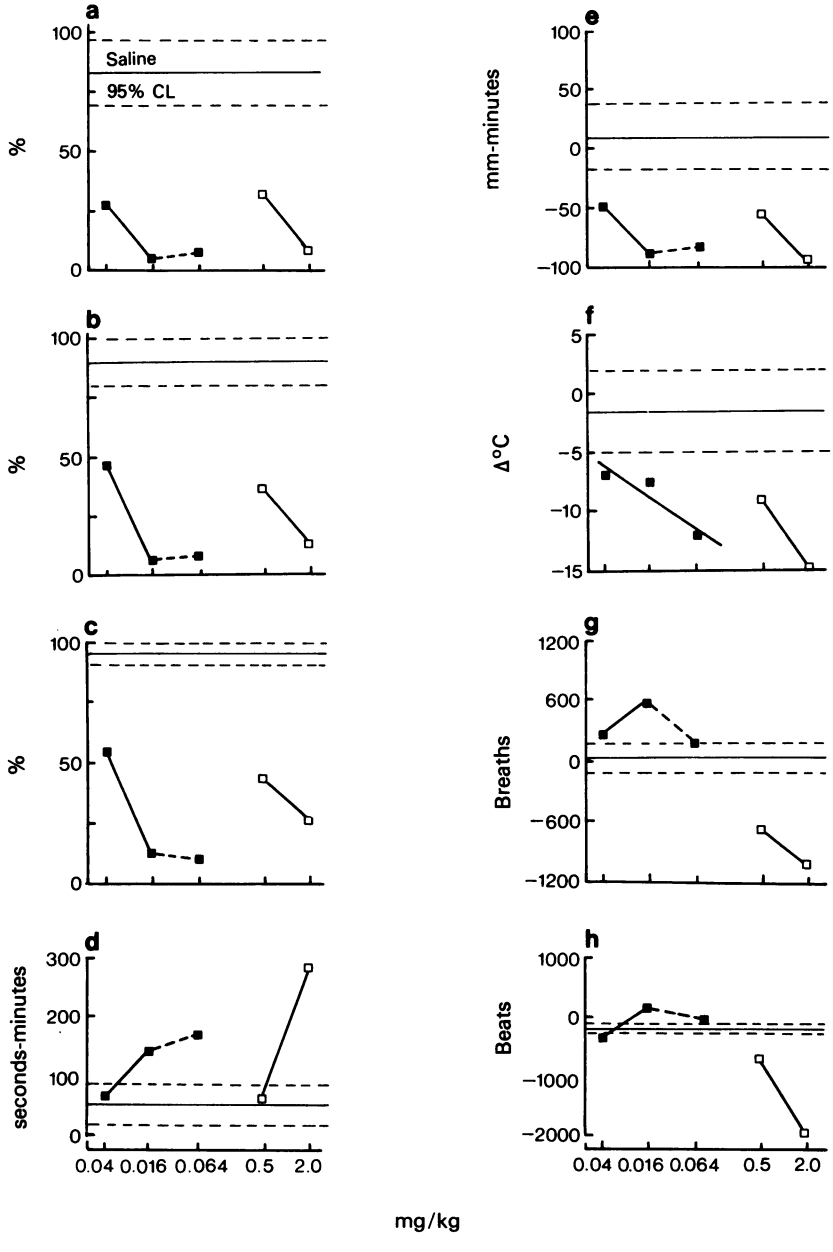


**Figure 3** Effects of buprenorphine (■) and morphine (□) in the chronic spinal dog. Each point represents the mean value obtained in six animals. Dotted portion of the dose-response curve represents the non-linear (plateau) portion of the partial agonist dose response line. (From Martin *et al.* 1976.) *a–h* as in Figure 1.

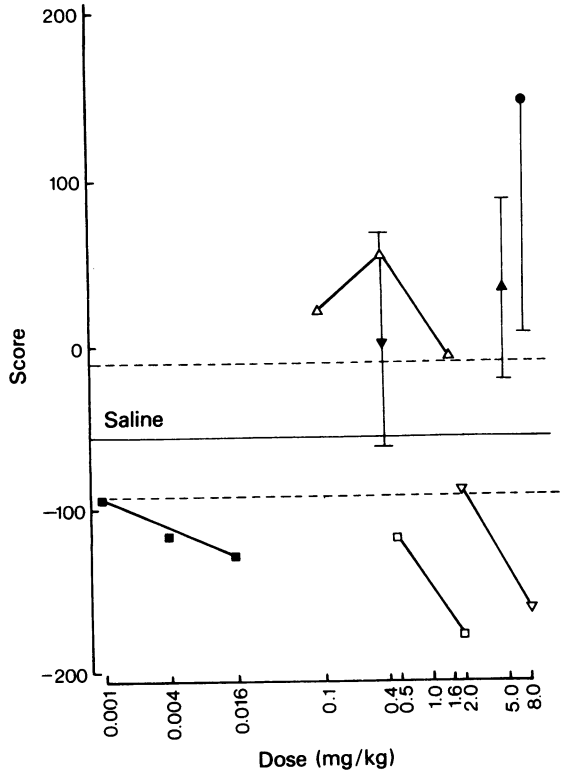


**Figure 4** Suppression of abstinence in morphine-dependent dogs. ■, Buprenorphine; □, morphine; ▽, D-propoxyphene; ▼, WIN 35, 197-2; △, ketocyclazocine; ▲, pentazocine; ●, apomorphine. Each point represents the mean of determinations made in six dogs. Bars represent 95% confidence limits of determinations. (From Martin *et al.* 1976.)

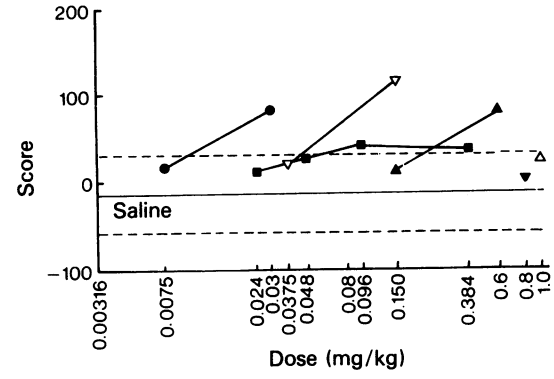


**Figure 5** Precipitation studies in the morphine-dependent dog. ●, Naloxone; ■, buprenorphine; ▲, N-methylcyclopropylnoroxycodone; ▼, WIN 35, 197-2; ▽, 6-β-hydroxynaltrexone; △, ketocyclazocine. Each point represents the mean of determinations made in six dogs. (From Martin *et al.* 1976.)

remarkable that in less than 20 years relatively selective agonists have been found and that competitive and partial agonists have been identified which have fulfilled the predictions of the receptor occupancy theory of drug action. The systematic search for nonaddicting and non-toxic analgesics, antitussives and antidiarrhoeal drugs, which began half a century ago, has borne fruit. The instigators of this programme had probably envisaged, in an empirical sense, that advances would be made by finding selective agents. To a degree this has occurred with the identification of multiple receptors and their associated agonists. It is only quite recently that the possibility of finding a morphine-like partial agonist has been envisaged. It has only been with buprenorphine that an analgesic has been discovered which has a sufficient degree of agonistic activity to produce a clinically desired effect, but not enough to produce a degree of physical dependence that would, in itself, give rise to drug-seeking behaviour.

The demonstration of the principles which are the basis for the actions of opioid agonists and antagonists has provided an impetus for a new chapter in neurochemistry, neurophysiology and neurotransmission. This marriage of good science and good therapeutics with all of its attending benefits should give heart, confidence, persistence and dedication to those who travel the road of experimental therapeutics.

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