Agonist and antagonist actions of narcotic analgesic drugs

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Preface

Although the opium alkaloids have been used for medicinal purposes since time immemorial, we still do not understand how these drugs and their modern counterparts exert their analgesic action and why they so readily produce psychological dependence and also severe physical dependence after a relatively short period of use. In recent years the interest in these drugs has risen steeply, chiefly because of the rapidly spreading non-medicinal use by persons who have become dependent on them. A great deal of effort has been spent by research workers in universities, research institutes and pharmaceutical firms to produce new compounds that retain their analgesic power but are not liable to be abused as drugs of addiction. Another important approach is an analysis of the factors that lead to psychological and physical dependence and to tolerance which appears to be associated with physical dependence.

At the Fourth International Pharmacological Congress held in Basle in 1969, some of the participants of the Congress who were interested in the pharmacology of narcotic analgesic drugs decided to have a short informal satellite session. At this meeting it was thought desirable to have an international symposium on the 'Agonist and antagonist actions of narcotic analgesic drugs' at the meeting of the British Pharmacological Society in Aberdeen in July 1971. This book is a record of the proceedings which covered the following aspects of the problem: chemistry, structure–activity relationships, acute and chronic effects, neurochemical mechanisms and psychological dependence.

I should like to express my thanks to the speakers and many guests, particularly to those who came from overseas. I am also grateful to the authorities of the University of Aberdeen who provided the necessary facilities and to the pharmaceutical companies who by their generous financial support made the Symposium possible. The contributors were Miles Laboratories, Reckitt & Colman and Sterling-Winthrop of the United Kingdom, and Bristol-Meyers Products, Eli Lilly & Co., Endo Laboratories, Merck Institute, Warner-Lambert Research Institute and Wyeth Laboratories of the United States.

Lastly, I should like to thank Dr. H. O. J. Collier and Dr. J. E. Villarreal, who kindly consented to help in the organization of the Symposium and to act as co-editors of this volume.

Aberdeen, August 1972 H. W. KOSTERLITZ.

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CHEMISTRY

Chairman
N. B. EDDY
Bethesda, Maryland, USA

Agonist–antagonists: an historical 'overview'

N. B. EDDY

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It is particularly appropriate that this agonist–antagonist symposium has been organized in Dr. Kosterlitz's department by Dr. Kosterlitz and Dr. Villarreal because of the work that they have initiated in differentiation and quantification of the agonist–antagonist components of many compounds. I am honoured and especially pleased to be invited to make the opening remarks because I have also had a part in the recognition of some aspects of simultaneous agonist–antagonist activity. A most interesting programme has been arranged for very detailed discussions, but, as background, I would like to present a brief historical 'overview'. Morphine and its derivatives have been known to display a dual effect since the earliest exploration of their pharmacology. Morphine is outstandingly depressant to the functions of the central nervous system but it can be excitatory in various ways and this excitatory action is the more prominent in some of the derivatives, indeed masking or antagonizing depressant effects under some circumstances. In the dual theory of tolerance advanced by Tatum, Seevers & Collins (1929) many years ago and revised in modified form by Seevers & Deneau (1962) some thirty years later, the depressant and excitatory effects have a different time course so that the latter outlasts and eventually submerges the former. Again, according to Tatum *et al.* (1929) monkeys given morphine might die after moderate doses (50–150 mg/kg) with signs of depression only, or after very large doses (300–500 mg/kg) with convulsions and exhaustion. The intermediate doses (200–300 mg/kg) caused no alarming symptoms; the excitatory effect of the drug presumably overcame, antagonized the depression. Furthermore, Gyang & Kosterlitz (1966) and Kosterlitz & Watt (1968) have reported that even morphine and codeine, though classed as agonists, have by his quantitative method a small antagonist component, somewhat greater in the case of codeine. Dual action then supplied for some a basic mechanism for antagonism. Perhaps we shall hear more of this theory later, certainly we shall hear of other mechanisms, but let me point out that thebaine, in which excitatory action is most pronounced, is not an overt antagonist (I don't know that it has been tested by Dr. Kosterlitz) and codeine which has an intermedi-

ate potential excitatory action, was said by Johannesson & Woods (1965) to enhance the analgesic effect of morphine.

We all know now, of course, that a different type of chemical modification, different, that is, from the change in thebaine and codeine, namely, substitution of allyl or various other groups for methyl on nitrogen of morphine or many morphine-like compounds brings out specific antagonist action, unbelievable as this seemed when it was first described by Pohl in 1914. Nearly thirty years later Leake did not find the idea unbelievable and proposed to his students, McCawley, Hart & March (1941) the synthesis of N-allylnormorphine, because he thought that incorporation into a molecule of a moiety of opposite action would permit persistence in the combination of the opposite action with antagonism of certain undesired effects. This is not generally true, a point on which Leake himself already had evidence in the morphine series, but happily N-allylnormorphine was a specific opiate antagonist.

The early studies of nalorphine confirmed its antagonist action, more or less across the range of morphine-like effects, and its specificity in respect to such effects. Some of us were discussing these points at the Addiction Research Center in the late 1940s together with a mechanism by which the antagonism might be brought about. I suggested, and the others agreed, that, if the antagonism were really specific, the result of the administration of nalorphine to a person in whom dependence of the morphine type had been established, should be the same as for abrupt withdrawal of morphine and an abstinence syndrome should emerge. Such was indeed the case (Wikler, Fraser & Isbell, 1953) and precipitation of abstinence signs by nalorphine shortly became a test for developing physical dependence.

The possibility of precipitation of abstinence phenomena through antagonist action seemed to preclude the development of tolerance and physical dependence to the antagonist, and early chronic administration experiments with nalorphine (Isbell, 1956) supported this hypothesis. However, in part, the doses used in these early experiments were insufficient and, in part, the observations were incomplete. Later it was shown that tolerance to the subjective effects of nalorphine and cross-tolerance to the subjective effects of other antagonists could develop, and some degree of a unique dependence which has been described as drug dependence of specific opiate antagonist type (Eddy & Martin, 1970), of which one characteristic is relatively little drug-seeking behaviour.

The early studies of nalorphine also showed that it had some morphine-like effects. Some analgesic action was observed with the hot-plate method, enough to calculate an ED_{50}, and at the Addiction Research Center constriction of the pupil, some respiratory depression and a sequence of subjective effects were noted (Wikler *et al.*, 1953). The subjective effects varied with the individual and with the dose, from euphoric (morphine-like exhilaration and

relaxation) to sedative (barbiturate-like sleepiness, tiredness and grogginess) and then to dysphoric (uncontrolled racing thoughts, inability to concentrate, anxiety, apprehension and fear of impending death), a syndrome distinctly characteristic of nalorphine and other antagonists.

A further early observation related to quantitative differences in antagonism of different effects. For example, Fromherz & Pellmont (1952) reported that the respiratory depressant effect of levorphanol was more easily antagonized, required a smaller dose of levallorphan, than its analgesic action. This suggested to me that, if nalorphine and morphine were administered simultaneously, a ratio of one to the other might be found with which the analgesic action of morphine would persist but side-effects, especially respiratory depression, would diminish or not occur. Lasagna & Beecher (1954) and later Keats & Telford (1956) and Houde & Wallenstein (1956) tested the suggestion clinically. Analgesia was retained but side-effects were not reduced, in fact, they became unbearably disturbing in too many patients. Nalorphine alone, however, was, milligram for milligram as analgesic as morphine. Thus, we had an agonist–antagonist of proven potency in respect to both components and the possibility, in the making of related compounds, of better analgesia to side-effect to dependence ratios, in other words, the most promising lead to the long sought separation of desirable and undesirable morphine-like properties. So much for background; developments from it are the theme of this symposium.

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The relationship between structure and activity in the 6,14-*endo*ethenotetrahydrothebaine series of analgesics

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The preparation of several series of closely related complex derivatives of tetrahydrothebaine (I, R = Me) and tetrahydro-oripavine (I, R = H), of general structures (II) and (III) has been described in detail in the chemical literature, and some pharmacological properties of certain bases in the series have been the subject of communications in a number of journals (Lewis, Bentley & Cowan, 1971). The bases were originally synthesized in the hope that the rigidity of the molecules and presence on their periphery of a large substituent might so alter the acceptability of the compounds at receptors as profoundly to modify their biological activities. Owing to the ease with which modifications can be made at several points in the molecules, the bases of these series present a unique opportunity for the study of the relationship between chemical structure and analgesic activity.

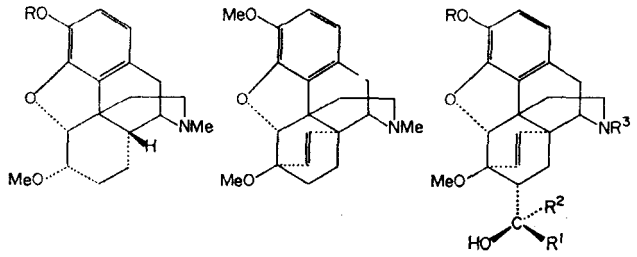
The parent compound of the series, 6,14-*endo*ethenotetrahydrothebaine can be regarded as a 6,14-ethano bridged derivative of codeine or a 6,14-etheno bridged derivative of B/C-*trans* dihydrocodeine and the increased complexity of the molecule leads to an increase in activity relative to both the B/C-*cis* and B/C-*trans* series, the compound II being 40 times more potent than morphine and 350 times more potent than B/C-*trans* morphine.

Most of the bases studied have the detailed stereochemistry shown in III, and are readily prepared as pure epimers. The results of variation at selected points in the molecules may be summarized as follows.

Variation in the size of R^1

The effect of varying the size of the group R^1 in a homologous series of bases (III) having constant substituents elsewhere is shown in Fig. 1* (R =

* In this and other figures in this paper analgesic potency is represented by the reciprocal of the ED_{50} measured in mol/kg, so as to compare bases of different molecular weight on a



(I) (II) (III)

R = Me:tetrahydrothebaine
R = H:tetrahydro-oripavine

Me) and Fig. 2 (R = H). The analgesic potency increases as the size of the group R^1 increases from H, through CH_3 and CH_2CH_3 to $CH_2CH_2CH_3$, after which further lengthening of the carbon chain leads to a progressive fall in activity. The same pattern of activity is observed for a range of values of NR^3 (Figs. 1 and 2) in which it will be noticed that the slopes of the curves are remarkably smooth. Certain members of the series in which R^3 is ethyl or propyl are not represented in Fig. 2 as the bases in question are morphine antagonists and cannot rationally be represented on a figure showing morphine-like analgesic activity. It may be emphasized, however, that simple morphine antagonists are not found in this series whatever the substituent on the nitrogen atom (R^3) when R^1 is other than a hydrogen atom or a methyl or ethyl group; when R^1 is greater than ethyl, apparent morphine-like analgesic activity is found, even in compounds bearing allyl and cyclopropylmethyl substituents, which are most commonly associated with morphine antagonists, on the nitrogen atom. The variation of activity with the size of R^1 in the series where R^3 is cyclopropylmethyl is shown in Figs. 1 and 2; the first three members of this series are morphine antagonists.

The patterns of activity in the related series of phenols (III, R = H) (Fig. 2) are essentially similar to those in the series in which R = CH_3, though the levels of activity are uniformly higher in the former than in the latter, and indeed the series of phenols contains the most potent analgesics, and the most potent morphine antagonists so far known. Morphine antagonist activity is again restricted to bases in which R^1 is H, CH_3 or C_2H_5. It can be argued that the phenols are the active species to which the methyl ethers are demethylated in the body, and that minor differences in activity pattern in the two groups (for example, the appearance of the phenols of peak activity where R^1 = C_4H_9 rather than C_3H_7 for two values of R^2) could be due to differences in the ease of demethylation or to differences in transport in certain cases.

fair basis, and so as to represent the most potent analgesics as peaks in the curves. The ED_{50} values were determined in rats by the tail-pressure method of Green & Young (1951), with administration of the drugs by the subcutaneous route.

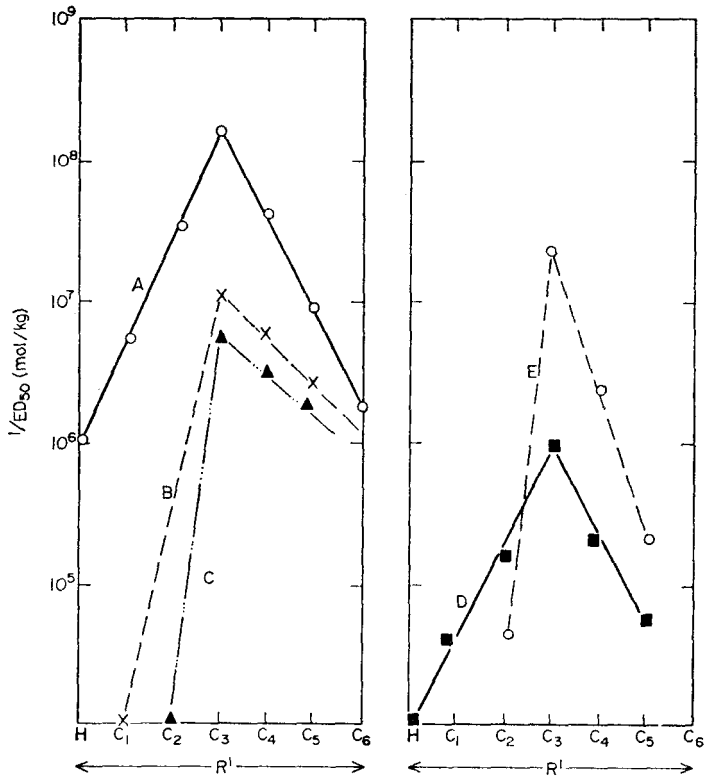


FIG. 1. Relationship between analgesic potency ($1/ED_{50}$) and size of Group R^1 for different values of R^3 in bases of formula III, R = Me, R^2 = Me. A, R^3 = Me; B, R^3 = Et; C, R^3 = *n*Pr; D, R^3 = *n*Bu; E, R^3 = cyclopropylmethyl.

In many cases the magnitude of changes in activity observed on lengthening the side-chain R^1 by a single carbon atom is so great that they lie well outside conceivable differences in brain concentrations and clearly specific receptor interactions must be involved (see below).

Reversal of stereochemistry at C-19

Variation of the group R^2 with constant R^1 at the asymmetric centre C-19 affords a series of bases, accessible chemically only with very great difficulty, in which, as far as they have been studied, analgesic activity appears to be independent of the size of R^2, apart from a general 10-fold drop in activity in going from R^2 = Me to R^2 = Et observed in the four homologous series where R^1 = Me, Et, Pr and Bu. These results, and those reported above, strongly suggest that the alcoholic group attached to C-7 is intimately associated with the receptor surface. If this group is bound to the receptor by the hydroxyl group, then with one arrangement at C-19 the group of variable

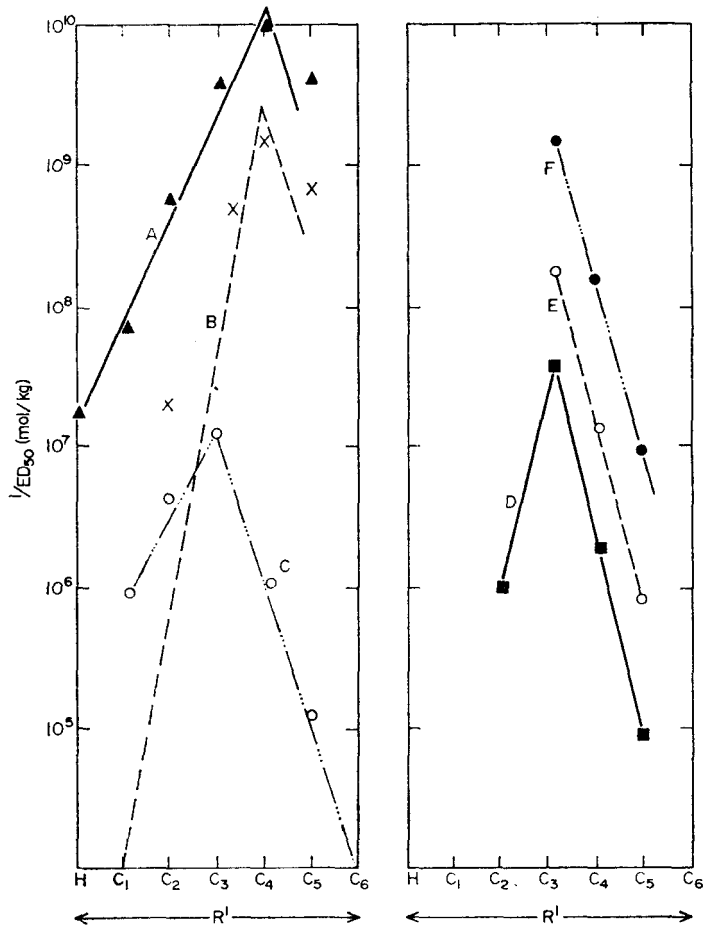


FIG. 2. Relationship between analgesic potency ($1/ED_{50}$) and size of group R^1 for different values of R^3 in bases of formula III, R = H, R^2 = Me. A, R^3 = Me; B, R^3 = Et; C, R^3 = *n*Am; D, R^3 = *n*Bu; E, R^3 = *n*Pr; F, R^3 = cyclopropylmethyl.

size, R^1, will be in contact with the receptor, and dependence of the activity on the nature of R^1 could reasonably be expected, whereas with the alternative stereochemistry the group of constant size will occupy that position, and clearly no relationship between activity and the nature of R^2 is to be expected.

Variation in the size of R^3

The effects of varying the size of R^3 can be discerned in Figs. 1 and 2, but are brought out more clearly in Figs. 3 and 4, in which potency is directly related to the size of R^3 for several values of R^1, R^2 remaining as CH_3 throughout. In general, it will be seen that analgesic activity decreases steadily