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Review

Electron-Transfer and Charge-Transfer Clastic Binding Hypotheses for Drug–Receptor Interactions

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The origins and development of clastic binding hypotheses for interaction of morphines with the opiate receptor and various hallucinogens with their putative receptors are reviewed. Possible alternative explanations of the facts which led to the clastic binding hypotheses are offered. Possible integration of the clastic binding processes into other, better-recognized processes at the receptors is considered.

KEY WORDS: receptors; clastic binding; opiates; hallucinogens; receptors; electron and charge transfer.

INTRODUCTION

The objective of this review is to summarize and critically examine several examples of electron-transfer and charge-transfer hypotheses for drug–receptor interactions. The examples of morphine-type opiates and various hallucinogens are emphasized. The electron- and charge-transfer processes at the receptor are referred to as clastic binding.

The term "clastic" binding was used by Belleau and Morgan (1) to describe a special kind of electron-transfer process at the opiate receptor. Namely, they proposed that morphine-type opiates achieve *productive* binding with the opiate receptor via a *stereospecific* electron transfer from the lone electron pair of opiates to some electrophilic site at the receptor. We use the term clastic binding in the same sense, namely, a stereospecific electron transfer from a drug which leads to a productive binding to the receptor, i.e., the binding which will elicit the primary biological response. In this review the "primary" biological response may include the main, desired response, e.g., analgesia of morphines, or an undesired side effect which cannot be dissociated from the desired response, e.g., euphoria of morphine drugs.

The word clastic comes from the Greek *klastos,* which means "broken." The usual use of this word is to designate an anatomical model with removable sections to show internal structure. This is exactly what we hope to accomplish in this review: to take a few selected electron-transfer interactions at the receptor and analyze them to discover the internal structure of such processes.

The electron-transfer reactions of various drugs are well documented in the studies of their biotransformations. For example, the metabolism of nitrogen-containing compounds has been shown to involve oxidative deamination, N-hydroxylation, N-oxidation, etc., all of which, at one stage or another, involve the electron-transfer processes (2). These metabolic electron-transfer processes, however, do not fit the definition of clastic binding, since the electron transfer involved is not responsible for the primary biological response of the drug. Thus, such electron-transfer processes are outside the scope of this review.

The most common electron-transfer reactions in the biological systems involve the participation of metal ions (3). The redox reactions, in which the metal ions serve as carriers of electrons, are well known (3). The metal ions can also act as complexing agents and as bridging and electron-transfer agents between one substrate and another (3). In this review we do not examine the electron-transfer processes that involve metal ions, since such processes are well understood and accepted and are reviewed in detail elsewhere.

In the initial stages of our discussion we use the term "electron transfer" to cover also the charge-transfer process. Namely, the latter process is an outer-sphere electron-transfer process in which no bonds are made or broken during the course of the reaction (4). The immediate effect of the outer-sphere electron transfer is the change in the charge of the reactants. Thus, these complexes are also called charge-transfer complexes. In the later parts of this review, when the specific cases of drug–receptor interactions are discussed, the electron-transfer processes are dissected into the inner- and outer-shell processes. [The inner-sphere electron transfers require the formation and rupture of bonds (4).]

In summary of this section, only selected cases of electron-transfer processes are discussed. With the exclusion of the electron transfers involved in the metabolic transformations and bioprocesses in which the participation of metal ions is proven, we are left with the electron-transfer processes which are usually suspected but not necessarily well proven. Here and there, one finds in the literature a paper or a cluster of papers in which some kind of clastic binding is proposed. Do all these papers demonstrate a common prin-

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ciple which can be successfully extracted and applied to drug–receptor interactions? Or do they represent a series of isolated, unconnected hypotheses? In this review we hope to provide some of the answers to these questions.

Figure 1 shows the structures of compounds discussed in this study.

THE ORIGINS AND DEVELOPMENT OF THE CLASTIC BINDING HYPOTHESIS FOR INTERACTION OF MORPHINES WITH THE OPIATE RECEPTOR

The electron-transfer clastic binding hypothesis was first proposed by Belleau and co-workers to explain the inverse deuterium isotope effects observed in substrate interactions with monoamine oxidases and dehydrogenases (5,6). Later, similar inverse deuterium isotope effects were observed in the case of morphine-type compounds (1). The latter effects were interpreted as evidence for clastic binding at the opiate receptor (1).

The phenomena of deuterium isotope effects and the significance of these effects in the formation of drug–receptor complexes are described in detail in Ref. 6. Here we present just one example from Ref. 1 to illustrate how the rationalization of the observed inverse deuterium isotope effect led to the clastic binding postulate.

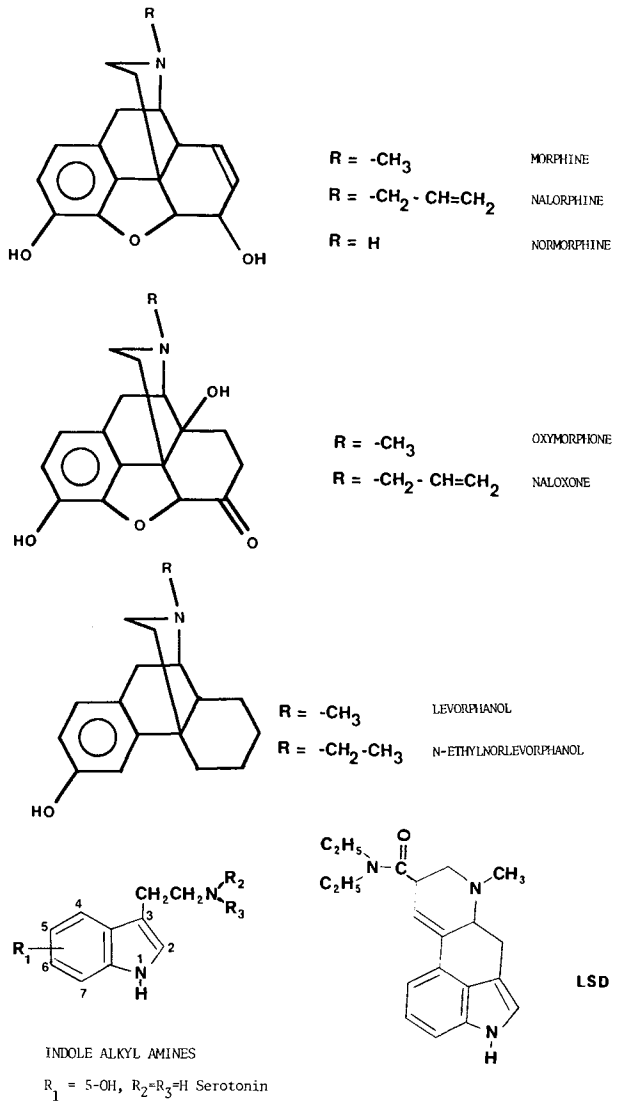


Fig. 1. Structures of compounds discussed in this study.

In the case of morphine, the N-CD_3 derivative exhibits a *decreased* analgesic potency by a factor of 1.64–3.00, depending on the route of administration. The N-CD_3 morphine is more basic by 0.12 pK_a units than its protio analogue, i.e., the N-CH_3 morphine. The increased basicity is expected to lead to a higher concentration of the protonated morphine, which may have an adverse effect on the rate of transport through the blood–brain barrier. Thus, a decreased activity of N-CD_3 morphine may be rationalized. Similarly, the N-CD_3 levorphanol is less active than its N-CH_3 analogue by a factor of 1.6. However, an opposite effect was observed in the N-ethyl levorphanol D and H analogues. This effect was found when the activity of N-ethyl (N-CH_2CH_3) levorphanol was compared to its deuterated analogue, N-CD_2CH_3 (i.e., the deuteration in the alpha position to nitrogen). Now the deuterated analogue was *more active* than its protio counterpart by a factor of 1.61. Therefore, the observed isotope effect in ethyl levorphanol is *inverse* as compared to levorphanol and morphine. Since the basicity factor in both deuterated morphine and deuterated ethyl levorphanol should be qualitatively the same, i.e., increased, one cannot invoke the basicity factor to explain this observed inverse isotope effect.

In order to rationalize the observed inverse isotope effects Belleau and co-workers postulated that, in principle, the receptor should be able to recognize D as opposed to H because of the smaller size of C–D vs C–H bonds and the different electronic properties of these two types of bonds. These authors ascribed to the opiate receptor an intrinsic and specific oxidative N-demethylase activity. Namely, the electron transfer occurs from the N-lone pair of morphine to the receptor and simultaneously the C–D or C–H bond of the carbon alpha to the nitrogen is being broken. This breaking of the bond would account for the observed isotope effect. The actual rate of the bond breaking would depend on the stereoelectronic fit of the N-alkyl group at the receptor. The N-CH_3 group would fit differently than the N-CH_2CH_3. Further, the well-established stereoelectronic specificity of various oxidases was invoked (1,6), which demands a favorable orientation of the N-lone pair and the N-alkyl group. The electron transfer from the N-lone pair to the receptor, in conjunction with the N-dealkylation, was termed clastic binding. This clastic binding was proposed to be responsible for analgesia and perhaps other biological effects of morphines (1).

This clastic binding hypothesis was further supported by the following findings by Fishman, Hahn, and co-workers about the N-dealkylation of morphines in the brain (7–10). The N-demethylation of morphine in the rat brain is localized in sites with a high opiate receptor content. Moreover, this N-demethylation was found to proceed in the brain only when pharmacological concentrations of the substrate were present, which indicated the biological significance of the reaction. The brain dealkylase involved in this N-demethylation was found to be different from that responsible for the same transformation in the liver (8). The brain demethylation of morphine was decreased by tolerance and by opiate antagonists, such as naloxone. The latter substance, which

is a pure opiate antagonist, was not dealkylated in the brain (9). Nalorphine, a mixed agonist–antagonist, is dealkylated in the brain but to a lesser extent than morphine, which is an agonist (10).

The N-dealkylation of morphines in the brain, which is described above, is undoubtedly biologically significant. However, it does not implicate that morphine *has to be* N-dealkylated to show its biological activity. One well-known example to illustrate that the N-dealkylation is not necessary for the activity is that of normorphine, an opiate agonist which does not possess an alkyl group on nitrogen (other than the elements of the piperidine ring).

However, the above-described lack of correlation between the biological activity and the possibility for the N-dealkylation does not compromise the clastic binding hypothesis. Namely, an extended electron transfer scheme proposed by Kolb (11) (Scheme I) encompasses all the cases as summarized below.

The N-dealkylation process involves pathway C in Scheme I. Initially, an electron is transferred from the nitrogen of morphine to the receptor to give the morphine radical cation. The latter undergoes a loss of proton from alpha position (pathway B), another electron transfer from nitrogen (pathway C), and hydrolysis by water to generate normorphine. The N-dealkylation, therefore, involves the transfer of *two* electrons from morphine to the receptor. This would be the classical electron transfer invoked by Belleau and Morgan (1) and Fishman, Hahn, and co-workers (7–10).

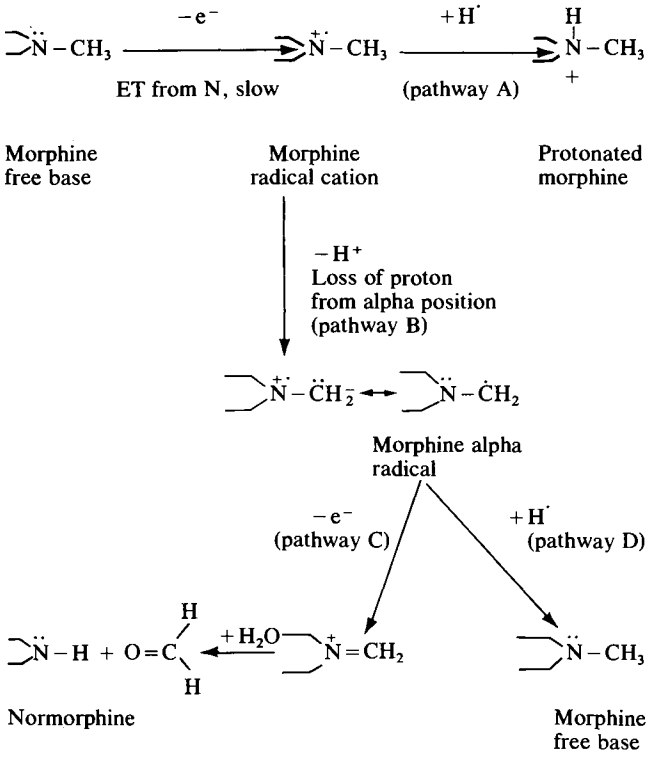
Scheme I, however, offers two chemically feasible pathways, A and D, by which morphine can give only *one* electron to the receptor and undergo transformations that would generate either protonated morphine (pathway A) or morphine free base (pathway D) but not normorphine. Initially, morphine free base gives one electron to the receptor to generate morphine radical cation. The latter may pick up a hydrogen atom from the receptor to give protonated morphine (pathway A) or may undergo the loss of a proton from the alpha position (pathway B) to give the morphine alpha radical. The latter radical can pick up a hydrogen atom from the receptor to give morphine free base (pathway D). In conclusion, the electron transfer from morphine does not have to lead the N-dealkylation, and therefore the activity of normorphine does not compromise the clastic binding process.

Hahn (10) proposed a hypothetical model of opiate action (Scheme II) in which the electron transfer step is postulated to precede and be crucial for the analgesic response.

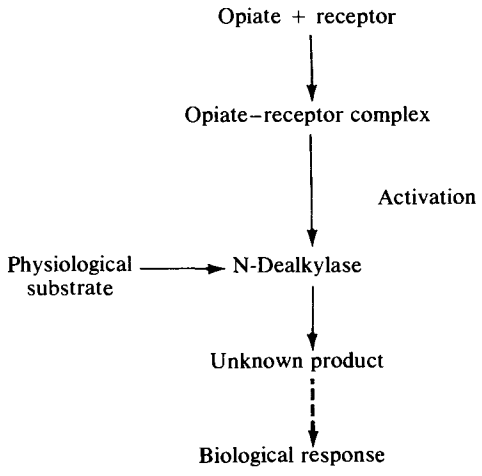
According to Hahn's model, the opiate, either endogenous or exogenous, binds to the receptor and forms the opiate–receptor complex. The latter provides for the activation of the N-dealkylase enzyme, whose actual function is uncertain. The activated N-dealkylase acts on an unknown physiological substrate to yield a product which ultimately leads to the analgesic response. The activation process was suggested to involve a protein kinase. The electron-transfer step is involved in N-dealkylation of the unknown physiological substrate, which is necessary for triggering the analgesic response. Narcotic antagonists, according to this model, bind to the receptor but fail to activate the enzyme.

THE ORIGINS AND DEVELOPMENT OF THE CLASTIC BINDING HYPOTHESIS FOR INTERACTIONS OF HALLUCINOGENS WITH THEIR RECEPTORS

The hallucinogenic activity of phenyl alkyl amines, indole alkyl amines, and LSD was first linked to the electron transfer ability of these drugs almost three decades ago (12,13). Hückel molecular orbital calculations of a series of hallucinogenic drugs and their nonhallucinogenic structural analogues indicated the close relationship between the HOMO (highest occupied molecular orbital) energy, an index of electron-donating ability, and the hallucinogenic potency (13). Based on these results, an electron donation model of interaction between hallucinogenic drugs and their



Scheme I



Scheme II

putative receptors was proposed (13). Later, a series of more sophisticated molecular orbital calculations confirmed the trends initially observed with the simple Hückel method (14). The HOMO energies of hallucinogens were also assessed experimentally, via measurements of ionization potentials (14–17) and charge-transfer capabilities (14) of these drugs. A good agreement was obtained between the calculated and the experimentally-deduced HOMO energies.

The electron-donating ability of hallucinogens was incorporated also into the QSAR (quantitative structure activity relationship) equations (14). However, other factors, such as hydrophobicity (expressed via log*P*), steric factors, etc., needed to be incorporated as well. The hallucinogenic activity data are of mixed quality (14,18). Some data are for humans, but most data are for animals in paradigms for LSD-like effects, for the activity at the serotonin receptor or its models, etc. Even data for humans carry an inherent error of 20–25%. Thus, the QSAR equations have a certain built-in error. Despite these errors, a clear trend emerged that in phenyl alkyl amines, indole alkyl amines, and LSD, both hydrophobicity and steric factors are crucial, while the electronic properties are important especially for phenyl alkyl amines. The existence of two receptors for hallucinogens was proposed based on these studies. One receptor would involve totally electronic interactions, while the other would involve totally hydrophobic interactions (14).

The mechanism of drug–receptor interaction is not necessarily obvious from various coefficients of the QSAR equations (19,20). Hence the main ideas concerning the *qualitative* nature of the relationship between the electronic properties and hallucinogenic activity are summarized below.

A charge transfer (CT) was proposed from the aromatic moiety of hallucinogens to the receptor. Both general CT and localized CT were considered. The latter was proposed especially in the case of indole alkyl amines (21). The localized CT was proposed to operate at the 4-position (21) or at the 4–5 bond of the indole ring (22). The sites of maximal polarizability were shown to be directly related to the localization of the HOMO of the molecules (22).

The importance of frontier orbital densities in the SAR of a series of indole alkyl amines was established (20). The structural requirements for the interaction with the receptor were successfully inferred from the electrostatic potential maps of these amines (20). The pattern of the electrostatic potentials of these drugs ("interaction pharmacophore") indicated the way the putative receptor sees these drugs (20). The electrostatic orientation vector of the indole portion of indole alkyl amines was found to be important for the recognition process of these drugs at the serotonin/LSD receptor (23).

It was calculated that the charge redistribution accompanying the formation of a complex of the aromatic indole moiety of the indole alkyl amines with a model receptor would involve little actual transfer of charge (20,24). Instead, the polarization within molecules of drug and model receptor would enhance the electrostatic interaction (20).

Based on a series of calculations cited above, a general model of the interaction of indole alkyl amines with the receptor emerged (20). In this model, the nitrogen-containing side chain, which is necessary for activity, is postulated to be anchored in its cationic form at an anionic site at the receptor. This anchoring imposes directionality with respect to which the indole portion can orient iself toward a polar site(s) at the receptor. The preferred orientation is that in which an optimal electrostatic interaction is achieved. The side chain reinforces the electrostatic nature of the interaction between the drug and the model receptor.

POSSIBLE ALTERNATIVE EXPLANATIONS OF THE FACTS THAT LED TO THE CLASTIC BINDING HYPOTHESES

The clastic binding hypothesis is much less developed in the case of hallucinogens than morphines. For this reason the former case is discussed first.

In hallucinogens the electron transfer is considered to be an outer-sphere, charge-transfer process. An overall electrostatic interaction with the receptor is envisioned as a result of the charge transfer from the aromatic portion of hallucinogens to their putative receptors. Although it is possible that electrons are actually injected to the receptor following the charge transfer formation, no evidence is available to support this. Moreover, it is not clear if the charge transfer process from the aromatic portion of hallucinogens qualifies for a true clastic binding. Namely, the latter (see Introduction) demands that the electron transfer is involved in the step which elicits the biological response. In the case of hallucinogens the charge transfer from the aromatic moiety makes an electrostatic interaction of this moiety with the receptor possible, but such an interaction may be just a component of the overall binding, a process in which the receptor recognizes and captures the drug. The nitrogen from the nonaromatic portion, such as the side chain (or its equivalent), which is believed to interact with the receptor in its protonated form, may carry more relative importance in eliciting the biological response than the aromatic moiety, although both are necessary for the activity. One could speculate, for example, that the role of the aromatic moiety is to anchor the drug to the receptor and that the biological response is triggered by, e.g., proton transfer from the nitrogen from the side chain to the receptor. As the putative receptors for hallucinogens become better defined, some of these questions may be answered.

In the case of morphines, biological data exist on inverse deuterium isotope effects (1) and N-dealkylation in the brain (7–10) which were interpreted by Belleau (1) and Fishman, Hahn, and co-workers (7–10) as evidence for an electron transfer mechanism at the opiate receptor (see The Origins and Development of the Clastic Binding Hypothesis for Interaction of Morphines with the Opiate Receptor).

Here, we explore some alternative explanations of the above biological data.

The inverse isotope effect of Belleau (1) can be accounted for without invoking the electron transfer. Instead, a more accepted proton-transfer mechanism for the opiate action (25–30) may be utilized. It is assumed that morphine binds to the receptor with its nitrogen in the protonated form. The positive charge on nitrogen is spread out on the N-methyl group to form a positive cationic head. This cationic head binds to a negatively charged binding site at the receptor. The latter site is termed "site C" in Refs. 29 and

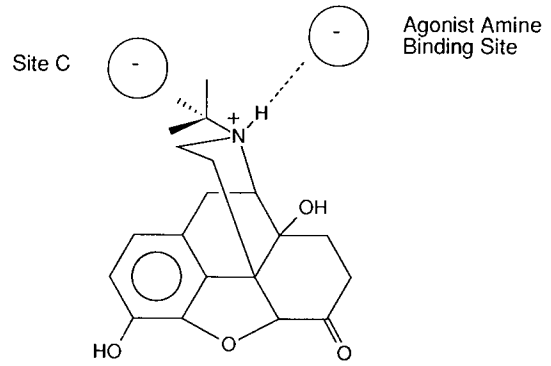


Fig. 2. Proton transfer between an opiate agonist (oxymorphone) and the receptor.

30 (Fig. 2). The proton from nitrogen is then transferred in a stereospecific manner to a negatively charged site at the receptor ("the agonist amine binding site" in Fig. 2). The antagonists bind to the receptor but cannot transfer proton to it, due to the steric hindrance to proton transfer imposed by the N-allyl (or similar) group (Fig. 3) (30). The utilization of this proton-transfer model and the assumption that the receptor is able to make a stereoelectronic distinction betwen deuterium (D) and hydrogen (H) at the cationic binding site (site C) leads to the following explanation of the inverse deuterium isotope effect.

The binding of the N-CH_2CH_3 compound is depicted in Fig. 4. The compound is shown in a conformation that allows binding of the partially positive H_1 and H_2 of the cationic head to the negative site at the receptor shown as a shaded area (equivalent to site C in Fig. 2). The CH_3 group may be crowding the cationic head and interfering with the binding of H_1 and H_2. This explanation is in agreement with the observed lower activity of the N-CH_2CH_3 compounds as compared to the N-CH_3 analogues (31). The crowded cationic head can accommodate D_1 and D_2 better than H_1 and H_2, because of smaller size and better electronic fit of the deuteriums. This explanation is supported by the observed steric isotope effects (32), smaller steric demand of D vs H (33), and electron-releasing inductive effect of D (33,34). In conclusion, a better stereoelectronic fit of the N-CD_2CH_3 compound may be responsible for its increased activity as compared to the N-CH_2CH_3 analogue, despite the increased basicity of the former compound, which should make it less active.

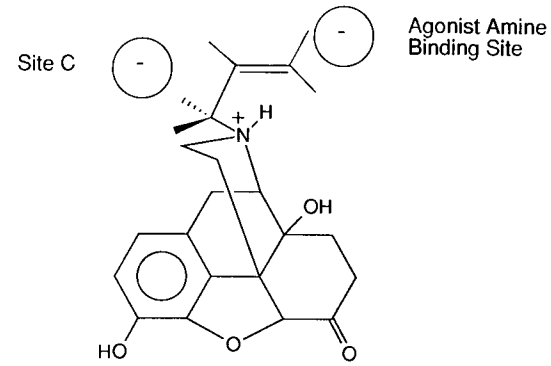


Fig. 3. The steric hindrance to proton transfer in a pure opiate antagonist (naloxone).

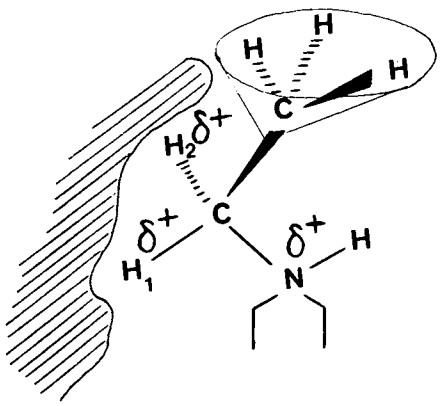


Fig. 4. Binding of the cationic head of an N-ethyl opiate agonist.

The case of the N-CH_3 compound is presented in Fig. 5. The H_3 is not crowding the cationic head. The uncrowded cationic head accommodates D_1–D_2 pretty much the same as H_1–H_2. The decreased activity of the N-CD_3 drug as compared to its protio analogue may be due to its increased basicity.

The clastic binding electron-transfer hypothesis of Fishman, Hahn, and co-workers (7–10) likewise can be challenged without challenging the experimental data based on which the hypothesis was proposed.

Scheme II (*vide supra*) of Hahn (10) invokes the electron transfer as the central process in the activation of the opiate–receptor complex. The analgesic response comes after the electron transfer and involves a hypothetical physiological substrate. We propose Scheme III below as a more likely sequence of steps that lead to the analgesic response. In Scheme III there is no need for a hypothetical physiological substrate.

In Scheme III, the opiate, endogenous or exogenous, binds to the opiate receptor and forms the opiate–receptor complex, just as in Scheme II. The conformation of the receptor within this opiate–receptor complex is conformation B, which is presumably different from the resting conformation A. Binding of both agonists and antagonists induces conformation B. However, only agonists can transfer a proton from their nitrogen to the receptor, a process which leads to the activation of the receptor and, ultimately, the analgesic response (30). The antagonists are unable to transfer the proton to the receptor, since their N-allyl (or other similar group) hinders the proton transfer (Fig. 3) (30).

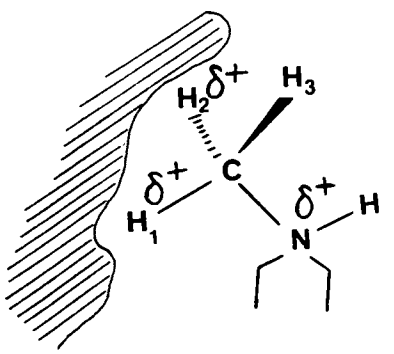
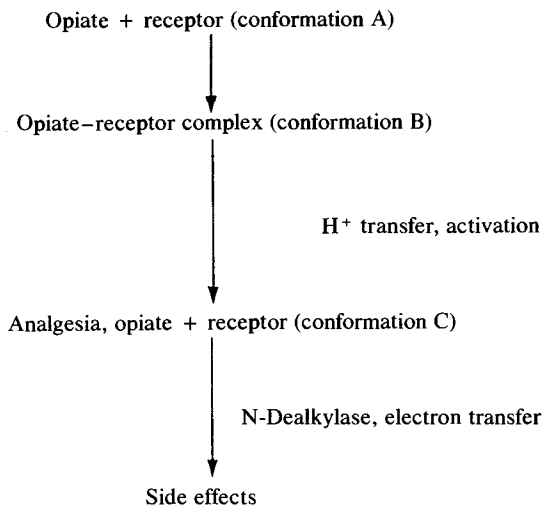


Fig. 5. Binding of the cationic head of an N-methyl opiate agonist.



Scheme III

After the proton is transferred, the opiate dissociates off the receptor, which is now presumably in conformation C, but is still in close proximity to the receptor. Conformation C of the receptor either unveils or otherwise activates the N-dealkylase, which acts on the opiate. This N-dealkylase activity may ultimately lead to side effects which normally cannot be dissociated from analgesia. Thus, the N-dealkylation measurements taken by Fishman, Hahn, and coworkers (7–10) may indeed parallel the analgesic response but may actually be occurring after the analgesic step.

In summary, Scheme III shows the possibility that the electron transfer N-dealkylase process at the receptor may occur at the receptor *after* the analgesic response is triggered by the proton transfer. Thus, the electron-transfer processes are *not the cause* of the analgesic response but occur *after the fact*. This is supported by the fact that the N-dealkylation happens only when pharmacological concentrations of morphine are used (8), since only then is the sufficient population of conformation C reached. Also, our approach explains why the antagonists are not dealkylated (9), and partial agonists, also possessing the N-allyl group, are (10). Namely, the antagonists are not able to transfer the proton and thus induce conformation C, at which the N-dealkylation occurs. The partial agonists, such as nalorphine, transfer protons to a small extent, since the steric hindrance for proton transfer is not complete (30). This is in accordance with the above-cited biological data on N-dealkylation of nalorphine (10).

While the electron transfer processes at conformation C are not linked to analgesia in this analysis, it is quite possible that they are responsible for some important side effects which are concurrent with analgesia, such as euphoria. One can only speculate about the details of N-dealkylation at the receptor. However, it appears worthwhile to investigate these electron-transfer processes in more detail, since they may be responsible for some secondary and undesirable effects of morphine analgesia.

ACKNOWLEDGMENT

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